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Angiogenic MicroRNAs Linked to Incidence and Progression of Diabetic Retinopathy in Type 1 Diabetes

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ABSTRACT

Circulating microRNAs (miRNAs) have emerged as novel biomarkers of diabetes. The present study focuses on the role of circulating miRNAs in patients with type 1 diabetes and their association with diabetic retinopathy. A total of 29 miRNAs were quantified in serum samples (n=300) using a nested case-control study design in two prospective cohorts of the Diabetic Retinopathy Candesartan Trial (DIRECT programme): PROTECT-1 and PREVENT-1. The PREVENT-1 trial included patients without retinopathy at baseline; the PROTECT-1 trial included patients with non-proliferative retinopathy at baseline. Two miRNAs previously implicated in angiogenesis, miR-27b and miR-320a, were associated with incidence and with progression of retinopathy: the odds ratio per standard deviation higher miR-27b was 0.57 (95%CI: 0.40, 0.82; P=0.002) in PREVENT-1, 0.78 (0.57, 1.07; P=0.124) in PROTECT-1, and 0.67 (0.50, 0.92; P=0.012) combined. The respective odds ratios for miR-320a were 1.57 (1.07, 2.31; P=0.020), 1.43 (1.05, 1.94; P=0.021), and 1.48 (1.17, 1.88; P=0.001). Proteomics analyses in endothelial cells returned the anti-angiogenic protein thrombospondin-1 as a common target of both miRNAs. Our study identifies two angiogenic miRNAs, miR-320a and miR-27b, as potential biomarkers for diabetic retinopathy.

Keywords: Retinopathy / Angiogenesis / Vascular / Proteomics / Endothelial Cell(s) / Biomarkers

Recent studies have begun to unveil a powerful and unexpected role of microRNAs (miRNAs) in numerous forms of diseases, providing a unique opportunity to translate this knowledge into the clinical setting in the form of miRNA-based therapeutics and diagnostics (1-2). MiRNAs are small non-coding RNAs with cell-type specific expression patterns that orchestrate biological networks by modulating gene expression. MiRNAs form base pairs with their target messenger RNAs and mediate gene silencing, often regulating multiple proteins within the same biological pathways. Given their importance in angiogenesis, along with the technical feasibility in manipulating their function *in vivo*, vascular miRNAs have become central targets for therapeutic manipulation, including diabetes (3).

Additionally, miRNAs circulate in blood. We have previously performed the first systematic analysis of circulating miRNAs in a population-based study (the Bruneck Study) and identified distinct miRNA signatures associated with type 2 diabetes (4) and risk of myocardial infarction (5). We have also highlighted their platelet origin (6) and applied concepts of network topology to explore their biomarker potential (7). Exciting opportunities exist to pursue miRNAs as novel biomarkers for risk estimation and patient stratification (8).

The present study addresses the role of circulating miRNAs in patients with type 1 diabetes (T1D) and their association to microvascular complications, in particular diabetic retinopathy. Our aims were three-fold: First, to evaluate whether miRNA profiles are independently associated with retinopathy development and progression in diabetes; Second, to quantify the incremental discriminatory power of miRNAs over and above traditional risk markers; Third, to conduct experiments using endothelial cells and proteomics profiling to provide mechanistic insight.

RESEARCH DESIGN AND METHODS

Patient sample. The DIabetic REtinopathy Candesartan Trials (DIRECT) trials have been described in detail elsewhere (9). In brief, two randomised, double-blind, parallel-design, and placebo-controlled trials (PREVENT-1 and PROTECT-1) were conducted in 309 centers worldwide. Both trials assigned patients with normotensive, normoalbuminuric T1D to either candesartan 16mg once a day or placebo. Exclusion criteria were eye conditions that precluded capture of gradable retinal photographs (i.e., open-angle glaucoma, dense cataract obscuring retinal view), stenotic valvular disease, previous history of heart attack or stroke, pregnancy, lactation, or renal impairment (serum creatinine ≥110μmol/L for women, ≥130μmol/l for men). The PREVENT-1 trial included patients without retinopathy at baseline (defined as Early Treatment Diabetic Retinopathy Study [ETDRS] scale level 10/10); the PROTECT-1 trial included patients with non-proliferative retinopathy at baseline (defined as ETDRS scale between 20/10 up to 47/47). For the present study, we used a "nested" case-control approach. Incident cases were defined as patients who progressed three steps or more on the ETDRS scale over the course of the study. Cases were stratum matched with controls, on sex, HbA_{1c} categories, and categories of diabetes duration (plus an ETDRS summary score in PROTECT-1). These were randomly selected from participants whose ETDRS scale did not progress and who remained free of intermittent microalbuminuria to the end of the study period. Numbers selected for analysis were 70 cases and 70 controls in PREVENT-1, and 93 cases and 93 controls in PROTECT-1. Analysis of miRNAs could not be performed on all serum samples. Thus, the number of cases and controls in the present analysis was 62 and 64 in PREVENT-1 and 81 and 93 in PROTECT-1 (n=300).

MiRNA measurements. Total RNA from 200µL of serum samples was prepared using the miRNeasy kit (Qiagen) as described previously (4). A fixed volume of 3µl of the 25µL RNA eluate was used as input for reverse transcriptase (RT) reactions using Megaplex Primer Pools (Human Pools A v2.1, Life Technologies). RT reaction products were further amplified using the Megaplex PreAmp Primers (Primers A v2.1). Taqman miRNA assays were used to assess the expression of individual miRNA. 0.5µL diluted pre-amplification product were combined with 0.25µL Taqman miRNA Assay (20x) (Life Technologies) and 2.5µL Taqman Universal PCR Master Mix No AmpErase UNG (2x) to a final volume of 5µL. qPCR was performed on an Life Technologies Viia7 thermocycler at 95°C for 10 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min. All samples were run in duplicates. Relative quantification was performed using the DataAssist v3.01 (Life Technologies). For normalization purposes, the average of all miRNA targets displaying Ct<32 cycles or an exogenous miRNA (*cel*-miR-39) spiked-in during RNA extraction were applied, as described previously (5).

Transfection. Human umbilical vein endothelial cells (HUVECs) were cultured as described previously (10) and seeded at 60-70% confluency on the day before transfection. Cells were washed in serum-free Dulbecco's Modified Eagle Medium (DMEM) and replaced with M199 containing EC supplement without antibiotics or serum. Human retinal microvascular endothelial cells (HRECs, obtained from Cell systems, Kirkland US) were seeded on CSC attachment factor (4Z0-210) and cultured in CSC complete media (4Z0-500). Prior to transfection HRECs were washed with CSC Serum Free Medium without antibiotics (SF-4Z0-500). MiRNA mimics or nontargeting mimic control (MC) were transfected at a final concentration of 50nmol/L using Lipofectamine™ RMAiMAX (Invitrogen) according to the manufacturer's recommendations (11).

Proteomic profiling of the endothelial secretome. HUVECs were carefully washed in serum-free medium and then incubated twice in fresh serum-free M199 for 30 min. Cells were stimulated in phorbol 12-myristate 13-acetate (PMA, 50nmol/L) containing M199 medium for 45 min and analysed by mass spectrometry as described previously (10). The conditioned medium was collected, centrifuged at 1000rpm for 5 min and concentrated using Amicon 3kD MWCO 15ml spin columns (Millipore) to 135µL. Then 0.5M Tris, 1% SDS, pH 8.8 (15µL) and 100mmol/L of DTT reducing agent (7.8µL) were added under agitation for 1 hr at 55°C, followed by incubation with 500mmol/L iodoacetamide (8.3µl) for 1 hr before precipitation with cold acetone (-20°C) overnight at -20°C. Samples were centrifuged (14000rpm, 10 min), the supernatant was discarded and the protein pellet left to air-dry. Pellets were re-suspended in 0.1mol/L, pH 8.5, triethylammonium bicarbonate (100µL) and incubated at 37°C under agitation for 30 min. Proteins were digested in 0.4µg/µl trypsin (1µL) overnight at 37°C. The reaction was stopped by addition of 10% formic acid (50µL). Peptide samples were purified using C18 spin columns (Thermo-Scientific). The eluate was kept at -80°C before freeze drying (Christ Alpha 1-2 LD Freeze Dryer) under vacuum at -55°C. The samples were re-suspended in 2% acetonitrile, 0.1% formic acid (20µl) and analyzed by reverse-phase nanoflow high performance liquid chromatography (Acclaim® PepMapC18, 3 µmole/L, 100Å, 50cm x 75µm inner diameter column (Thermo Scientific) interfaced with a Q Exactive Plus Orbitrap mass spectrometer (Thermo Scientific). Each sample was separated at a flow rate of 0.3 µl/min over 4 hrs as follows: 0-10 min / 2%-10%B, 10-200 min / 10%-30%B, 200-210 min / 30%-40%B, 210-220 min / 99%B, 220-240 min / 2%B, where A=0.1% formic acid in ddH_2O and B=80% acetonitrile, 0.1% formic acid in ddH_2O. Samples were subject to a full MS scan over m/z range from 350-1600, whereby the 15 most abundant peaks were selected for tandem mass spectrometry and fragmented by higher energy collisional dissociation.

Database search. Raw data were analysed by Mascot and Sequest HT algorithms (Proteome Discoverer 1.4) to identify proteins against Swissprot protein database (version 201401) with taxonomy set to all entries, precursor mass tolerance 10 ppm, fragment mass tolerance 20 mmu, oxidation of methionine as a variable modification and carbamidomethylation of cysteine as a static modification, and a maximum of two missed cleavage sites permitted. Search results were loaded onto Scaffold software (version 4.3), where a protein probability > 99%, a peptide probability > 95% and a minimum number of two peptides per protein were applied as filters to generate the list of identified proteins.

Luciferase reporter assays. The 3' untranslated region of the human NRP1 and SEMA6A harboring a putative binding site for miR-320a and miR-27b respectively, were cloned into the XhoI and PmeI linkers of the dual-luciferase reporter vector psiCheck2 (Promega). The following primer sets were used:

NPR; F: TTCAATGAGTATGGCCGACA,

NPR; R: GGATTTCGCTCAGTTTCC,

SEMA6A; F: CGCACAGAGGTGAACAGAAA,

SEMA6A; R: GCCCAACATGGCATTTATCT.

The reporter constructs (100ng) were transfected together with their respective miRNA mimics (50nmol/L) or MC in triplicate into HUVECs, previously plated (post-12 hrs) in 6-well plates using lipofectamine RNAiMAX (Invitrogen) as described above. After 48 hrs, cells were harvested in 200μL Glo Lysis Buffer (Promega) and the activities of both Renilla and firefly were measured. 30μL of each lysate were analysed using Dual-Glo Luciferase reagents (Promega). Renilla luciferase activity was normalised to constitutive firefly luciferase activity for each well.

Enzyme-linked immunosorbent assay (ELISAs). Thrombospondin-1 levels in the conditioned media were determined using the Human Thrombospondin-1 Quantikine ELISA Kit (Bio-Techne) according to the manufacturer's instruction.

Statistical analysis. MiRNA values were log-transformed for analysis. Pair-wise correlations between miRNAs and other markers were assessed using Pearson correlation coefficients in a pooled dataset of 145 controls, and plotted with the R package 'corrplot' using hierarchical clustering and the single linkage method. We analysed the association of miRNAs with incident retinopathy in two steps. First, to identify the miRNA subset with the highest prognostic ability for future retinopathy, we used a L_1-penalized logistic regression technique. This method helps prevent overfitting of collinear and high-dimensional data and implements the 'least absolute shrinkage and selection operator' (LASSO) algorithm, shrinking regression coefficients towards zero relative to the maximum likelihood estimates. The amount of shrinkage is determined by the tuning parameter λ_1, which is progressively increased up to the value that shrinks all regression coefficients to zero. We estimated the optimal tuning parameter λ_1 as the median of ten thousand 5-fold likelihood cross-validations. Plots of beta coefficients (y-axis) versus λ_1 (x-axis) were generated using the R package 'penalized'. Sensitivity analyses were conducted that (i) standardized miRNA concentrations to a global Ct average (instead of to *Cel* miR-39) and (ii) excluded participants from analysis with diabetic nephropathy or microalbuminuria. Because the LASSO method allows assessment of relevance and robustness of individual explanatory variables but produces biased estimates of beta coefficients, we fitted, as a second step, 'traditional' logistic regression models for identified miRNAs. Analyses were adjusted for age, sex and diastolic blood pressure, and conducted separately for the two trials. A pooled estimate of association was calculated with random-effects meta-analysis. Between-study heterogeneity

was assessed by the I^2 statistic (12). Regarding the experimental studies, results are presented as the mean±S.E.M. For results from transfected ECs, paired or unpaired Student t-test, one-way ANOVA with Dunnetts or Tukey's post-hoc analysis, and two-way ANOVAs were performed using GraphPad prism 5 software. With allowance for loss due to missing miRNA measurement, our sample size allowed us to detect a difference in retinopathy incidence and in progression in association with a standardized difference of 0.4 and 0.5 respectively for any given miRNA signal with 80% power and 5% significance. Analysis was performed using R 3.1.3 statistical software (13) and Stata 12.1 MP, with two-sided tests and $P<0.05$.

RESULTS

Associations of miRNAs with incidence and progression of retinopathy in the DIRECT trials. From the PREVENT-1 and PROTECT-1 trials of a total of 3326 participants with T1D, we selected 62 patients with incident diabetes retinopathy, 93 patients with progressive diabetes retinopathy, and 145 matched controls. **Supplementary Table 1** compares clinical characteristics of participants selected for the nested case-control analysis and those not selected. A panel of 29 miRNAs, of which some were previously shown to be associated with T2D (4) and CVD (5), were measured in serum and values were standardized to an exogenous spike-in normalization control, *Cel* miR-39. Baseline characteristics of study participants are summarized in **Table 1**. The ratio of males to females, and mean diabetes duration, was similar in cases and controls within each trial, as anticipated due to matching. Mean HbA_{1c}, however, was a little higher in controls, reflecting the fact that cases and controls were stratum, rather than individually matched by HbA_{1c}. Differences in age and blood pressure levels were also observed in the two study populations. The complex correlation patterns of serum miRNAs and baseline characteristics are depicted in **Fig. 1**. MiRNAs emerged to be highly correlated with each other, but largely independent from other characteristics such as age, duration of diabetes, blood pressure and HbA_{1c}.

We conducted penalized logistic regression analyses adjusted for age, sex and diastolic blood pressure were conducted to identify and evaluate the association of miRNAs with incidence and progression of diabetic retinopathy (**Fig. 2, Supplementary Fig. 1**). The descriptive tables in **Fig. 2** show the direction of association and the percentage of cross-validated models that included the respective miRNA. The following miRNAs were identified in descending order of importance: miR-27b, miR-320a, miR-454, and miR-28-3p in PREVENT-1; and miR-320a, miR-122, miR-221, and miR-27b in PROTECT-1.

Generally, these miRNAs were more commonly selected for inclusion in cross-validated models for incidence than for progression of diabetic retinopathy (>90% vs. >10%). Results for all 29 individual miRNAs are provided in **Supplementary Fig. 2**, but should be interpreted with caution in light of multiple testing and type-1 error.

Since combinations of miRNAs can be superior to individual miRNAs (4, 5, 7), we then performed 'traditional' logistic regression for the two miRNAs most consistently associated with incidence and progression of diabetic retinopathy: miR-27b and miR-320a. **Fig. 3** shows estimates of associations for miR-27b and miR-320a adjusted for each other, age, sex and diastolic blood pressure. The odds ratio per standard deviation higher miR-27b was 0.57 (95%CI: 0.40, 0.82; P=0.002) in PREVENT-1, 0.78 (0.57, 1.07; P=0.124) in PROTECT-1, and 0.67 (0.50, 0.92; P=0.012) combined. The respective odds ratios for miR-320a were 1.57 (1.07, 2.31; P=0.020), 1.43 (1.05, 1.94; P=0.021), and 1.48 (1.17, 1.88; P=0.001). Qualitatively similar results were observed in analyses that (i) standardized miRNA levels to a C_t-average of all miRNAs (instead of standardization to spiked in *Cel miR-39,* **Supplementary Fig. 3**); (ii) excluded cases with incident microalbuminuria (**Supplementary Fig. 3**); (iii) used different levels of adjustment (unadjusted; age, sex and systolic blood pressure or HbA_{1c}); or (iv) omitted outliers of the miRNA distributions. **Supplementary Fig. 4** summarizes raw values of miR-27b and miR-320a for cases and controls. Addition of information on miR-27b and miR-320a to a model a panel of variables associated with disease risk (i.e., age, sex, duration of diabetes, diastolic blood pressure, and level of HbA_{1c}) improved the area under the receiver operating curve by 0.087 for PREVENT-1 (P=0.027) and by 0.034 for PROTECT-1 (P=0.214) (**Supplementary Fig. 5**).

Expression of miRNAs in endothelial cells. A PCR comparison was conducted to compare the endogenous expression of miR-27b and miR-320a to abundant endothelial miRNAs (miR-126 and miR-126* or miR-126-3p and miR-126-5p, respectively). There was

no major difference in the endogenous miRNA expression of miR-27b, miR-320a, miR-126-3p and miR-126-5p between four different types of ECs: human saphenous vein endothelial cells (HSaVEC), human aortic endothelial cells (HAoEC), human retinal endothelial cells (HRECs) and HUVECs (**Supplementary Table 2**). Notably, miR-320a was consistently more abundant in endothelial cells than miR-27b. Next, mimics for miR-27b and miR-320a were co-transfected with luciferase reporter constructs containing putative binding site of two confirmed target proteins for miR-27b and miR-320a: semaphorin-6A (SEMA6A) and neuropilin-1 (NRP1), respectively. SEMA6A is a negative regulator of MAPK signaling, known to increase transcription of angiogenic effector genes (14). NRP1 is a co-receptor for VEGF and semaphorin, promoting EC proliferation and microvessel density (15). 48 hrs after transfection, luciferase activity was found to be decreased by approximately 30% and 40% in SEMA6A and NRP1, respectively (**Fig. 4*A, B***). Thereby the functionality of miRNA mimics was confirmed through silencing expression of known targets.

Proteomics for miRNA target identification. We have demonstrated recently that direct and indirect targets can be identified in a broader proteomics screen, including targets that would not have been anticipated based on current bioinformatics prediction models (11, 16). To complement our clinical studies, we used a proteomics approach to identify putative protein targets of miR-27b and miR-320a in the secretome of endothelial cells. HUVECs were stimulated with PMA to induce exocytosis of Weibel-Palade bodies, an endothelial-cell specific storage organelle, allowing for protein analysis by mass spectrometry. Among over 650 proteins identified (**Supplementary Table 3**), only thrombospondin-1 (TSP-1) showed differential secretion from both miR-27b and miR-320a transfected endothelial cells, relative to control transfected cells (**Fig. 4*C, D***). The proteomics data were independently validated by ELISA (**Fig. 5*A***). Similar results were obtained in HRECs following miR-27b or miR-320a overexpression (**Fig. 5*B***). An alignment of the thrombospondin-1 gene (*THBS-1*)

mRNA region with the sequence of miR-320a and miR-27b is shown in **Fig. 6*A***. The vertical bars and bold characters indicate sequences of the miR-320a and miR-27b binding site of the *THBS-1* target gene. As expected for direct miRNA targets, there was complementarity between the miR-27b seed-matching sequence and the 3′-UTR region of the *THBS-1* target gene. According to one algorithm (miRWalk), TSP-1 was also predicted as a target for miR-320a. The putative seed binding region, however, was within the coding region of the *THBS-1* gene. To further confirm the functionality of these predicted interactions, we fused the putative binding regions within the *THBS-1* target gene to a luciferase reporter vector. Co-expression of synthetic miR-27b, but not miR-320a decreased *THBS-1* reporter activity (data not shown), confirming TSP-1 as a direct target of miR-27b (17) and an indirect target of miR-320a (**Fig. 6*B***).

DISCUSSION

Using data from two independent prospective cohorts, we identified miR-27b and miR-320a as potential biomarkers for new onset or progression of retinopathy in patients with T1D. Both miR-27 and miR-320a have previously associated with metabolic syndrome and type 2 diabetes (18) and implicated in angiogenesis, providing a mechanistic underpinning for the observed association with diabetic retinopathy in the DIRECT cohort (9).

Retinopathy in T1D. Retinopathy remains the most frequent, and most feared complication of T1D (19). It is associated with elevated risks of other diabetes complications, notably nephropathy and cardiovascular disease (20). Although acknowledged as a vascular phenomenon, the only intervention proven to date to reduce onset or progression of retinopathy is tight glycaemic control. This is difficult to achieve, and is associated with elevated risks of hypoglycaemic episodes. Significant numbers of individuals with T1D continue to progress to severe, possibly sight-threatening disease even in the presence of good glycaemic control. There is therefore a need to discover novel biomarkers, which identify individuals at high risk of progressive retinopathy, and targets for therapeutic intervention.

MiRNAs in T1D. MiRNAs may offer distinct advantages over other biomarkers (8): Unlike messenger RNAs, miRNAs are stable in blood. As nucleic acids, miRNAs can be measured by qPCR methodology allowing the multiplexing of several miRNAs in a single experiment. Thus far, the role of miRNAs in diabetic retinopathy progression has been assessed in small animal models (21-26). Moreover, a miRNA dependent cross-talk between HIF1α and VEGF was reported in the diabetic retina (27). In this study, we show that miR-320a and miR-27b are associated with new onset or progression of retinopathy in patients

with T1D. These findings were unaltered by excluding participants with incident persistent or intermittent microalbuminuria at any time during the follow up.

Mechanistic links to angiogenesis. Besides its potential prognostic and diagnostic value, miRNAs may participate in an unexplored mechanism contributing to retinopathy in patients with T1D. Several miRNAs can target the same effector. Diverse miRNAs can also act cooperatively or redundantly to regulate the effectors of the same biological process. MiR-320a regulates glycolysis and represses angiogenic factors, including Flk1, VEGFc, IGF-1, IGF-1R and FGF (28-29). MiR-320a has also been implicated in tumor angiogenesis by silencing neuropilin-1 (30). MiR-27b is thought to promote angiogenesis by targeting anti-angiogenic genes (31), including the transmembrane protein, semaphorin-6A. The miR-23/-27/-24 gene clusters are enriched in endothelial cells and highly vascularized tissues (32). MiR-27b orchestrates endothelial tip cell formation (33-34). By analysing protein targets of miR-27b and miR-320a in endothelial cells, we obtained a more comprehensive depiction of the interactions and regulatory feedback loops between angiogenic proteins and our candidate miRNAs.

Proteomics approach for miRNA target identification. The "targetome" of most miRNAs remains an unexplored aspect of current biology. Currently, the available miRNA target prediction tools are based on an incomplete understanding of miRNA target recognition and miRNA efficacy. Bioinformatic methodologies reveal numerous putative targets, but only 1 out of 5 of the *in silico* predictions is correct and experimental confirmation is essential. Proteomics methods can be useful for identifying miRNA targets at the protein level in addition to the use of bioinformatics prediction algorithms. We have pursued a proteomics approach to compare the effects of miR-27b and miR-320a on the secretome of endothelial cells (10). TSP-1 was returned as a common target of both miR-27b and miR320a (35). TSP-1 is an extracellular matrix protein, which inhibits EC proliferation,

migration and angiogenesis (36). Its anti-angiogenic effect is mediated through an interaction with VEGF, specifically via inhibition of VEGF receptor-2 activation through engaging its receptor CD47 (37). This has further been supported *in-vivo*, specifically in the eye: depletion of TSP-1 resulted in corneal neovascularisation in mice (38). Of particular significance to diabetic retinopathy, a biphasic response of TSP-1 mediated through VEGF occurred in microvascular cells in the ischemic retina (39). This response tightly regulates VEGF and therefore indicates a potential negative feedback mechanism of VEGF-induced angiogenesis through TSP-1 (39). By now, several studies have implicated TSP-1 in pathological angiogenesis in the retina (40-42). TSP-1 has been shown to inhibit neovascularisation in diabetic mice (43). Moreover, miR-27b rescued impaired angiogenesis via TSP-1 suppression (17). Our findings confirm that miR-27b directly suppresses reporter activity for TSP-1. In contrast, miR-320a has an indirect effect on TSP-1 secretion.

Strengths and limitations of the study. Our study was prospective and hence measured miRNA levels before occurrence of the disease outcome. Using a nested case-control approach, we identified 155 participants with retinopathy incidence/progression among DIRECT trial participants (overall n=3326) and compared miRNA profiles to those of matched controls. Associations were independent of established risk factors for diabetic retinopathy, including age, sex, HbA_{1c}, diabetes duration and blood pressure, and were further underpinned by our biologically-plausible finding from the proteomics analysis that both miRNAs target thrombospondin-1. Still, whether miR-27b and miR-320a are causally involved in diabetes retinopathy or a marker of this disease remains to be clarified. The identified miRNAs are not retina specific. The changes in miR-27b and miR-320a may reflect a systemic predisposition for pathological angiogenesis. The cause for the differential regulation of circulating levels of miR-27b and miR-320a is currently unclear. For many biomarkers, the cellular origin remains uncertain. For example, both endothelial cells as well

as platelets secrete TSP-1. Measuring its circulating levels does not reveal how much of TSP-1 is endothelial- or platelet-derived. The same limitation applies to miRNAs that are not tissue specific and detected in the circulation. Both miR-320a and miR-27b are also present in platelets (6). The opposing directionality of the association of miR-27b and miR-320a with diabetic retinopathy could hint to a different cellular origin of these two circulating miRNAs, i.e. miR-320a is secreted at much higher levels from endothelial cells than miR-27b. Further studies are required to provide an in depth understanding of their cellular origin and to test the diagnostic or therapeutic potential of these two circulating miRNAs in diabetic retinopathy. We measured miRNA levels only at baseline and hence could not assess nor take into account within-person variability of the miRNAs over time. Finally, model selection and parameter estimation were performed on the same dataset without adjustment, which may lead to an overestimation of the strength of association obtained and underestimation of confidence limits.

Conclusions. Understanding how circulating miRNAs could be harnessed for assessing the risk of retinopathy in T1D is an essential area of research. Our data in the DIRECT trials show that miR-320a and miR-27b are associated with new onset and progression of retinopathy. Besides identifying circulating miRNAs associated with retinopathy, we also interrogated the targets of miR-27b and miR-320a in endothelial cells using a proteomics approach. Taken together, our study is the first to identify miRNA biomarkers for retinopathy in two independent cohorts. These findings await confirmation in larger studies but our two lead miRNAs may have clinical utility given their established links to angiogenesis, including the translational control of TSP-1 by miR-27b and its reduced endothelial secretion by miR-320a.

Author contribution: NC, RK, and MM conceived and designed the experiments; AZ, SB, and XY performed the experiments; PW, SL, SK, and NC, analyzed the data; PR provided the serum samples; AZ, PW, NC and MM wrote the manuscript. MM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest: King's College London has filed patent applications on miRNA biomarkers. Otherwise, no conflicts of interest relevant to this article were reported.

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FIGURE LEGENDS

FIG. 1. Pair-wise Pearson correlation coefficients of serum miRNA concentrations and other markers. Abbreviations: DBP, diastolic blood pressure; HbA_{1c}, haemoglobin A1c; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; UAER, urinary albumin excretion rate.

FIG. 2. Penalized logistic regression analysis of the associations of 29 serum miRNA concentrations with diabetic retinopathy. Association with incident diabetic retinopathy in PREVENT-1 (A). Association with progression of diabetic retinopathy in PROTECT-1 (B). Models included age, sex and diastolic blood pressure as unpenalized covariates. The graph shows beta coefficients for different levels of penalization (λ_1, estimated in 100 steps) and is truncated at a λ_1 of 3, hence not all measured miRNAs are plotted. The black dashed line indicates the optimal tuning parameter λ_1 evaluated using ten thousand 5-fold likelihood cross-validations. The descriptive table shows the direction of association and the percentage of cross-validated models that included the respective miRNA.

FIG. 3. Standard logistic regression analysis and meta-analysis of the association of miR-27b and miR-320a with diabetic retinopathy and TSP-1 as common target in endothelial cells. Association of miR-27b and miR-320a with diabetic retinopathy in PREVENT-1, PROTECT-1, and both studies combined. Associations of miR-27b and miR-320a with diabetic retinopathy were adjusted for each other, plus age, sex, and diastolic blood pressure. Standard deviations were defined in controls. Study-specific results were combined using random-effects meta-analysis.

FIG. 4. Proteomics for miRNA target identification. Luciferase reporter assays to confirm functional miRNA mimics. Suppression of semaphorin-6A (A), a known target of miR-27b, and neuropilin-1 (B), a target of miR-320a. Spectral counts of thrombospondin-1 as quantified by mass spectrometry in the secretome of miR-27b (C) and miR-320a (D) transfected endothelial cells compared to mimic controls. Error bars represent SEM. * denotes $p<0.05$ in 3 independent experiments, ** $P<0.01$.

FIG. 5. Validation of the proteomics findings by ELISA. Reduced secretion of thrombospondin-1 (TSP1) in the endothelial secretome upon transfection with mimics of miR-27b and miR-320a. (A) HUVECs following 45min of PMA stimulation in serum-free medium and (B) HRECs following overnight serum deprivation in the presence of endothelial supplements. * $P<0.05$.

FIG. 6. Angiogenic miRNAs. Alignment of thrombospondin-1 (THBS-1) mRNA region with miR-320a and miR-27b (A). Relative abundance of miR-320a and miR-27b in endothelial cells (EC) and suppression of TSP1 secretion as a shared molecular pathway (B). Circulating miRNA changes in patients with T1D and retinopathy, however, may represent markers of a milieu that is conducive to pathological angiogenesis rather than a local release from the retina.

Table 1. Baseline characteristics of the study populations.

Variable	PREVENT-1			PROTECT-1		
	Cases (n=62)	Controls (n=64)	P value*	Cases (n=93)	Controls (n=81)	P value*
	Mean (SD), median [IQR] or count (%)			Mean (SD), median [IQR] or count (%)		
Age at randomisation, years	31.1 (8.1)	27.7 (8.1)	0.02	31.5 (9.1)	31 (8.5)	0.7
Male sex	33 (53%)	37 (58%)	0.7	58 (62%)	42 (52%)	0.2
Duration of diabetes, years	7.3 (3.8)	7.3 (3.6)	1.0	10.9 (4.0)	10.6 (4.0)	0.7
Systolic blood pressure, mmHg	116 (9.1)	119 (9.6)	0.04	117 (10.8)	118 (8.9)	0.7
Diastolic blood pressure, mmHg	72 (7.7)	73 (6.5)	0.3	72.7 (7.0)	75 (6.4)	0.02
HbA_{1c}, %†	8.9 (1.5)	9.2 (1.8)	0.4	8.9 (1.2)	9.4 (1.5)	0.05
UAER, µg/min	4.8 [3.3, 6.5]	4.3 [3.5, 6.0]	0.4	5.0 [3.0, 6.5]	5.0 [3.5, 9.5]	0.2
WHR all	0.81 (0.07)	0.83 (0.09)	0.08	0.85 (0.08)	0.82 (0.08)	0.1
WHR men	0.84 (0.07)	0.88 (0.09)	0.03	0.88 (0.07)	0.88 (0.07)	0.4
WHR women	0.77 (0.05)	0.77 (0.05)	0.9	0.78 (0.07)	0.77 (0.07)	0.5
Creatinine, µmol/l	89.7 (13)	90.0 (14)	0.9	88.1 (13.8)	86.7 (14.1)	0.6
GFR*, ml/min/1.73m^2	88 [75,107]	90 [79,105]	0.8	92 [77,107]	94 [80,104]	0.8
GFR**, ml/min/1.73m^2	83 [71,96]	83 [73,98]	0.8	86 [73,100]	88 [75,96]	0.6
HDL cholesterol, mmol/l	1.7 (0.3)	1.7 (0.4)	0.6	1.7 (0.4)	1.8 (0.4)	0.07
Total cholesterol, mmol/l	4.7 (1.1)	4.9 (0.9)	0.5	5.1 (1.1)	4.9 (0.8)	0.2
Insulin dose, U/kg/day	0.77 (0.21)	0.69 (0.24)	0.07	0.81 (0.30)	0.71 (0.20)	0.01
eGDR*** mg/kg/min	9.2 (1.3)	9.0 (1.4)	0.4	8.6 (1.3)	9.1 (1.3)	0.02
Never smoker	34 (55)	47 (73)		50 (54)	54 (67)	
Ex smoker	7 (11)	2 (3)		5 (5)	8 (10)	
Current smoker	21 (34)	15 (24)	0.02	38 (41)	19 (23)	0.08

Abbreviations: HbA_{1c}, haemoglobin A_{1c}; IQR, interquartile range; SD, standard deviation; UAER, urinary albumin excretion rate; WHR, waist hip ratio; HDL, high-density lipoprotein. *P values were calculated using Fisher's exact tests for categorical variables, two-group t-tests for continuous normally-distributed variables, or Wilcoxon rank-sum tests for continuous left-skewed variables.

GFR* CKD-EPI (44)
GFR** MDRD4 (45)
eGDR*** estimated glucose disposal rate (46)

Figure 1.

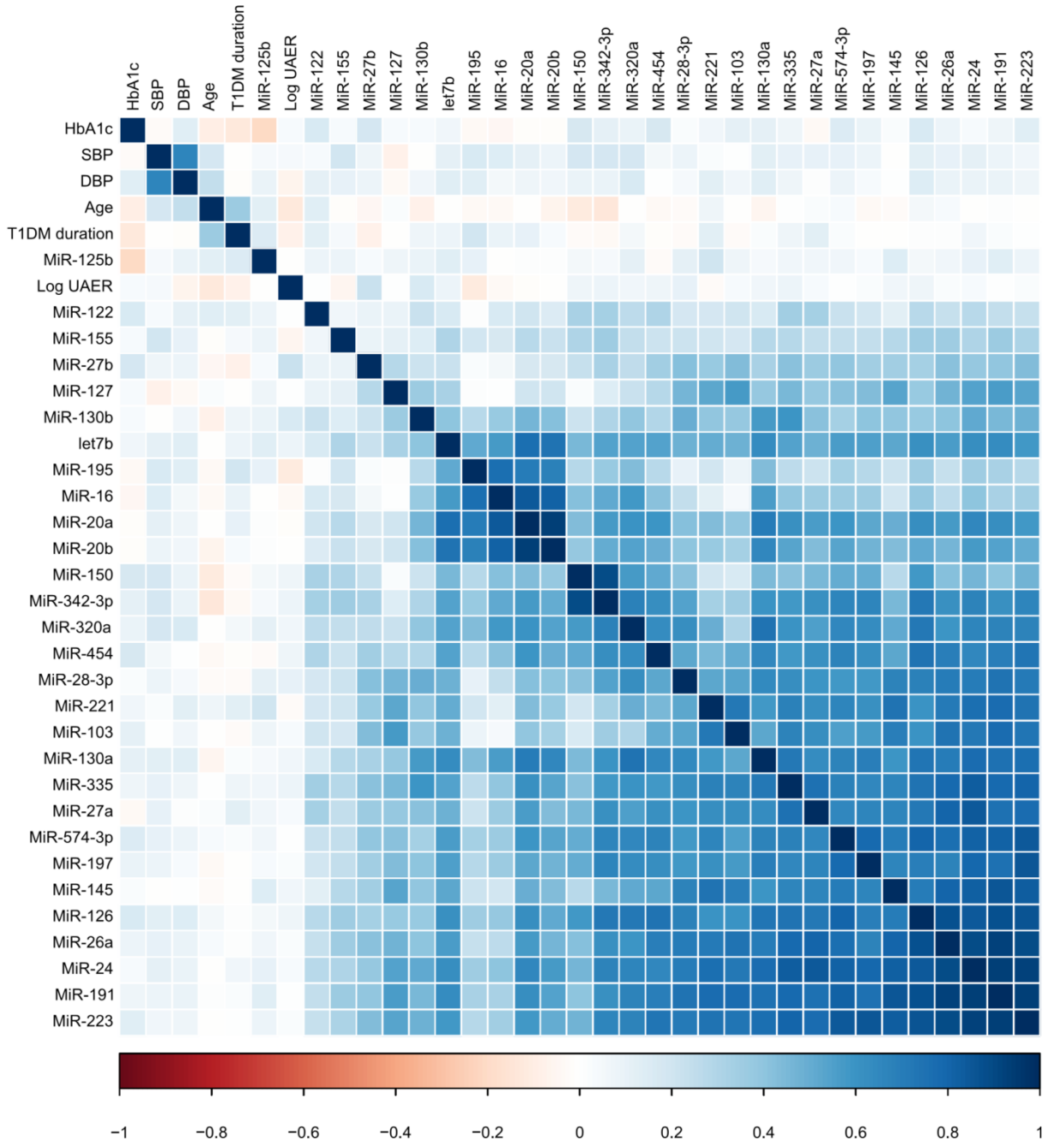
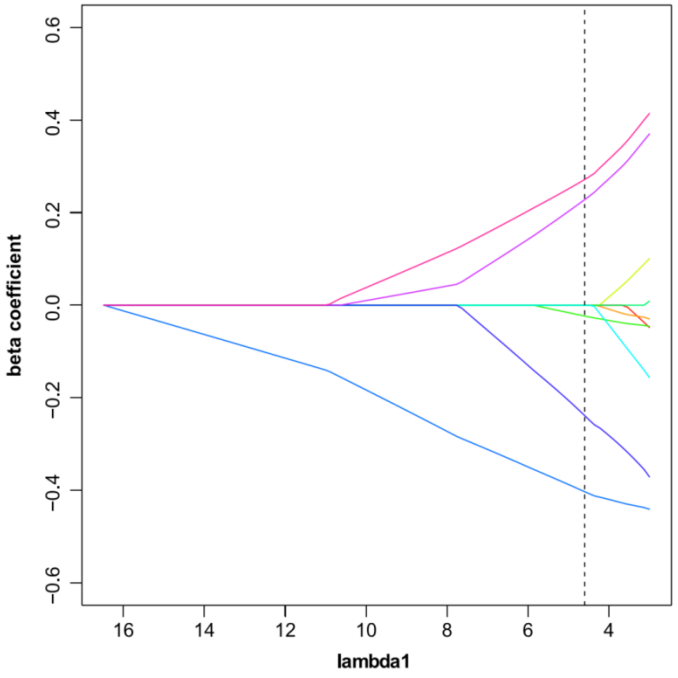

HbA1c
SBP
DBP
Age
T1DM duration
MiR-125b
Log UAER
MiR-122
MiR-155
MiR-27b
MiR-127
MiR-130b
let7b
MiR-195
MiR-16
MiR-20a
MiR-20b
MiR-150
MiR-342-3p
MiR-320a
MiR-454
MiR-28-3p
MiR-221
MiR-103
MiR-130a
MiR-335
MiR-27a
MiR-574-3p
MiR-197
MiR-145
MiR-126
MiR-26a
MiR-24
MiR-191
MiR-223
−1
−0.8
−0.6
−0.4
−0.2
0
0.2
0.4
0.6
0.8
1

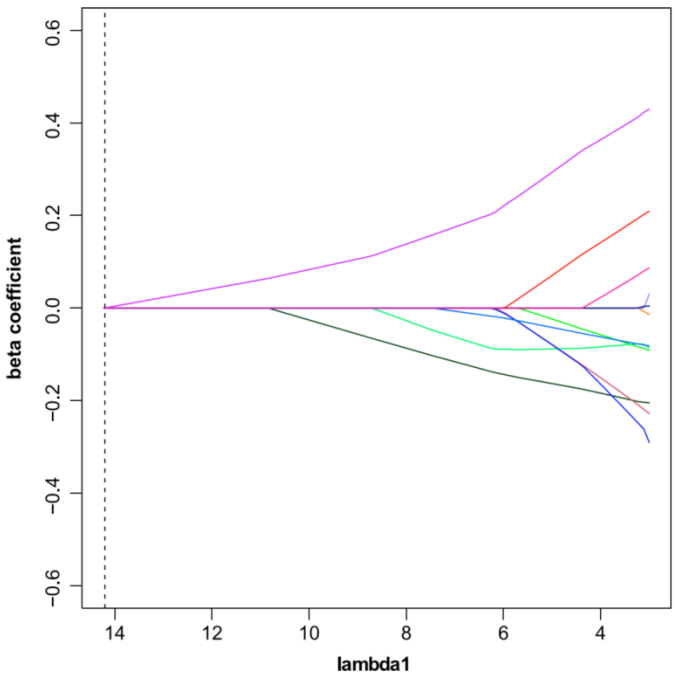
Figure 2.

(A) PREVENT-1



MicroRNA	Direction	Inclusion in model
MiR-27b	-	95%
MiR-320a	+	93%
MiR-454	+	93%
MiR-28-3p	-	91%
MiR-155	-	83%
MiR-27a	-	39%
MiR-127	-	37%
MiR-130b	+	33%
let7b	-	10%
MiR-221	+	3%

(B) PROTECT-1



MicroRNA	Direction	Inclusion in model
MiR-320a	+	50%
MiR-122	-	32%
MiR-221	-	19%
MiR-27b	-	14%
MiR-26a	-	8%
MiR-195	-	8%
let7b	+	7%
MiR-125b	-	5%
MiR-454	+	2%
MiR-20b	+	0.3%
MiR-150	-	0.3%
MiR-191	+	0.1%

Figure 3.

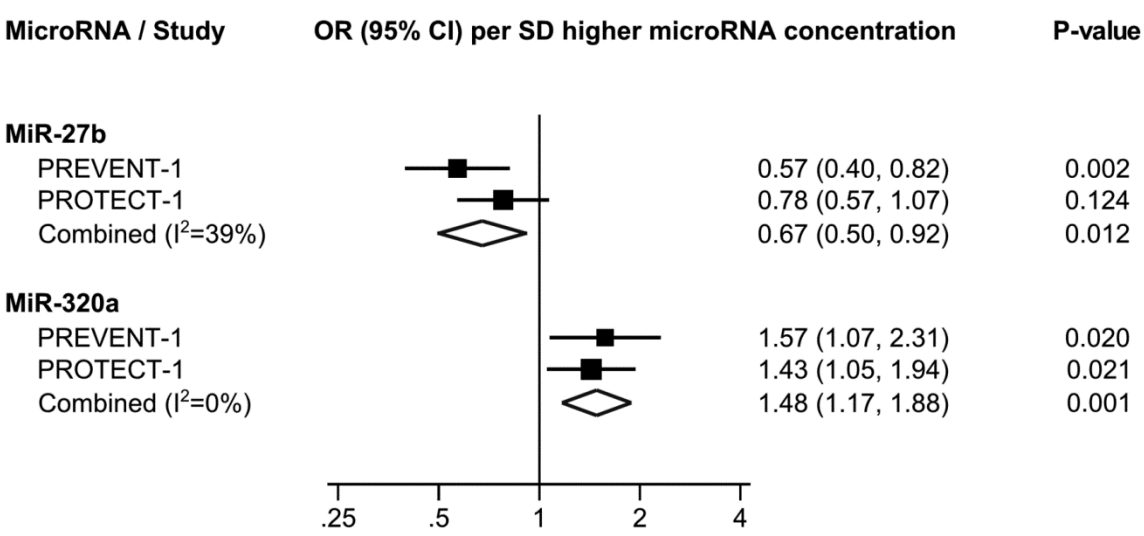

MicroRNA / Study
OR (95% CI) per SD higher microRNA concentration
P-value
MiR-27b
PREVENT-1
0.57 (0.40, 0.82)
0.002
PROTECT-1
0.78 (0.57, 1.07)
0.124
Combined (I2=39%)
0.67 (0.50, 0.92)
0.012
MiR-320a
PREVENT-1
1.57 (1.07, 2.31)
0.020
PROTECT-1
1.43 (1.05, 1.94)
0.021
Combined (I2=0%)
1.48 (1.17, 1.88)
0.001
.25
.5
1
2
4

Figure 4.

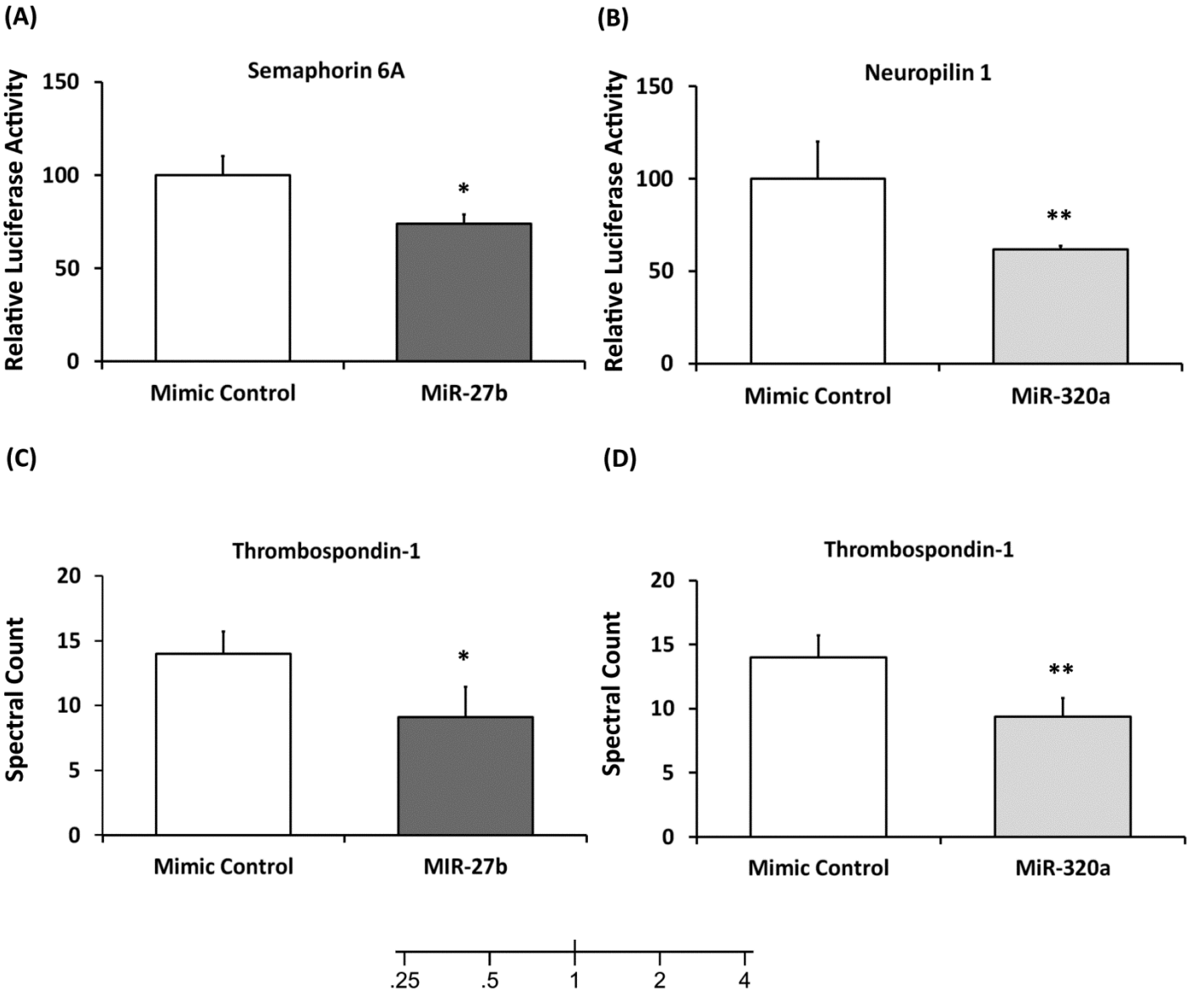

(A)
Semaphorin 6A
Relative Luciferase Activity
150
100
50
0
*
Mimic Control
MiR-27b
(B)
Neuropilin 1
Relative Luciferase Activity
150
100
50
0
**
Mimic Control
MiR-320a
(C)
Thrombospondin-1
Spectral Count
20
15
10
5
0
*
Mimic Control
MIR-27b
(D)
Thrombospondin-1
Spectral Count
20
15
10
5
0
**
Mimic Control
MiR-320a
.25
.5
1
2
4

Figure 5.

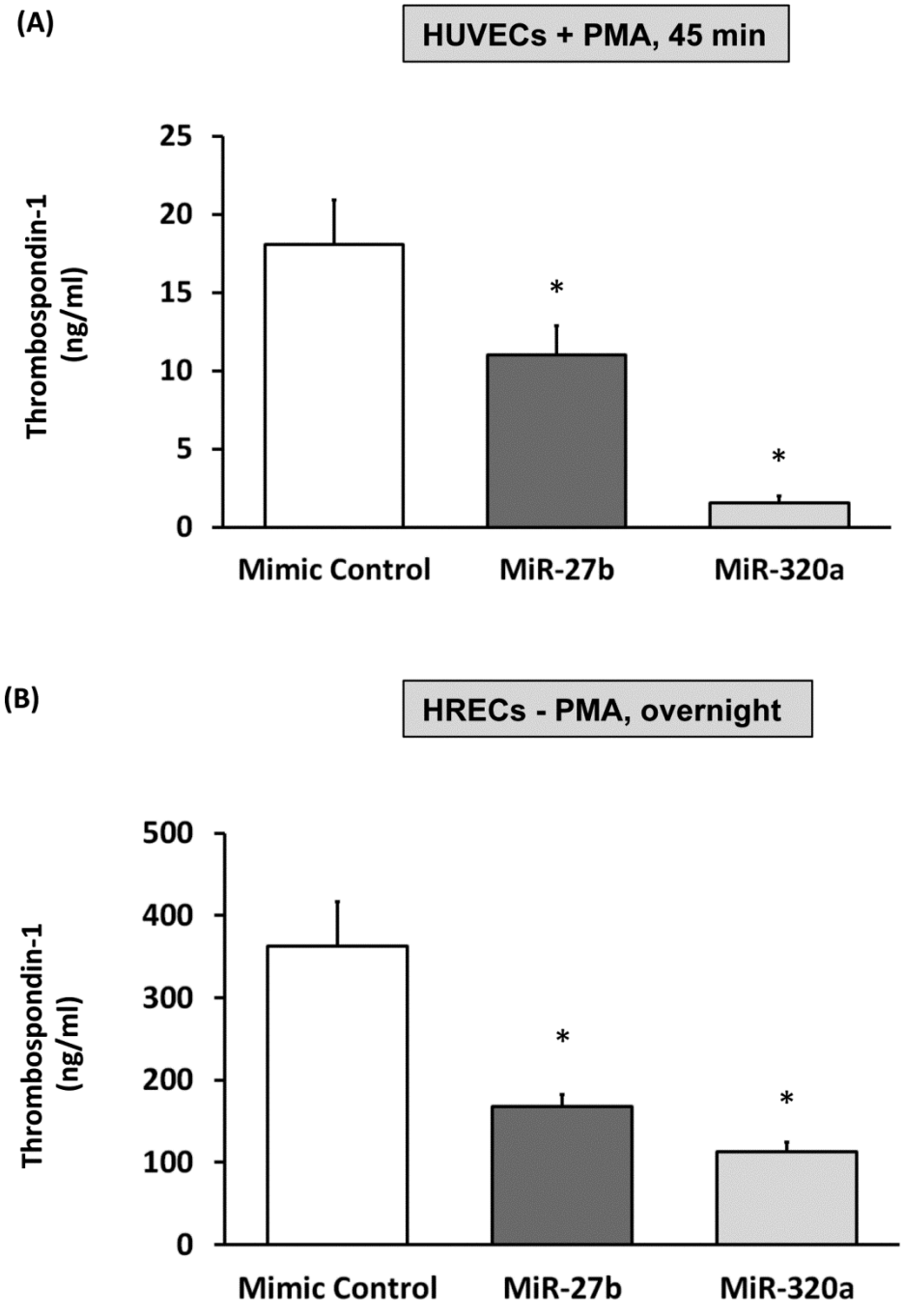
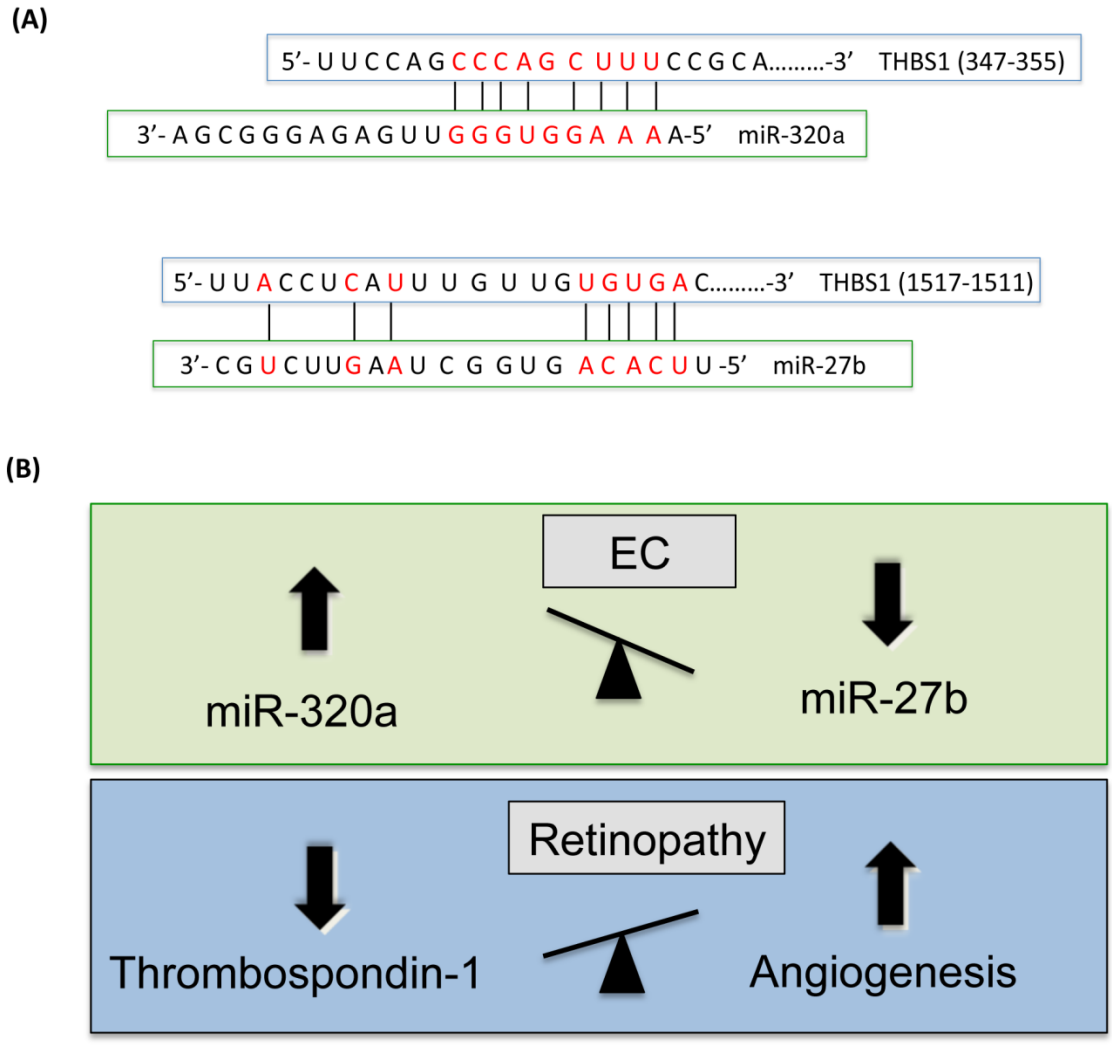

(A)
HUVECs + PMA, 45 min
Thrombospondin-1 (ng/ml)
25
20
15
10
5
0
*
*
Mimic Control
MiR-27b
MiR-320a
(B)
HRECs - PMA, overnight
Thrombospondin-1 (ng/ml)
500
400
300
200
100
0
*
*
Mimic Control
MiR-27b
MiR-320a

Figure 6.


(A)
5'- U U C C A G C C C A G C U U U C C G C A.....-3' THBS1 (347-355)
3'- A G C G G G A G A G U U G G G U G G A A A A-5' miR-320a
5'- U U A C C U C A U U U G U U G U G U G A C.....-3' THBS1 (1517-1511)
3'- C G U C U U G A A U C G G U G A C A C U U -5' miR-27b
(B)
EC
miR-320a
miR-27b
Retinopathy
Thrombospondin-1
Angiogenesis

SUPPLEMENTARY DATA

Angiogenic MicroRNAs Linked to Incidence and Progression of Diabetic Retinopathy in Type 1 Diabetes

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Supplementary Table: 3
Supplementary Figures: 5

Supplementary Table 1.
Comparison of selected cases and controls to the remainder of the study population.

Variable	PREVENT-1			PROTECT-1		
	Included	Not included	P value*	Included	Not included	P value*
	Mean (SD), median [IQR] or count (%)			Mean (SD), median [IQR] or count (%)		
N	126	1295		174	1731	
Age (yr)	29.4 (8.2)	29.8 (8.1)	0.6	31.2 (8.7)	31.7 (8.4)	0.4
Men	70 (56)	735 (57)	0.8	100 (57)	999 (57)	1.0
Duration (yr)	7.3 (3.7)	6.7 (3.9)	0.06	10.7 (4.0)	11.0 (4.3)	0.5
HbA_{1c} %	9.0 (1.7)	8.1 (1.7)	<0.0001	9.2 (1.4)	8.4 (1.6)	<0.0001
Systolic BP mmHg	118 (10)	116 (10)	0.1	118 (10)	117 (10)	0.5
Diastolic BP mmHg	73 (7)	72 (7)	0.8	74 (7)	74 (7)	0.5
UAER	4.5 [3.5, 6.5]	4.5 [3.0, 6.5]	0.4	5.0 [3.5, 7.0]	5.0 [3.5, 7.5]	0.4
BMI kg/m2	23.9 (3.4)	23.9 (3.3)	0.9	24.4 (3.4)	24.7 (3.6)	0.3
WHR all	0.82 (0.08)	0.83 (0.09)	0.3	0.84 (0.08)	0.84 (0.09)	0.3
WHR men	0.86 (0.08)	0.87 (0.08)	0.5	0.88 (0.07)	0.89 (0.07)	0.3
WHR women	0.77 (0.05)	0.78 (0.07)	0.4	0.78 (0.07)	0.79 (0.07)	0.4
Creatinine µmol/L	89.8 (13.4)	89.8 (14.1)	1.0	87.4 (13.3)	91.1 (13.7)	0.01
GFR* ml/min/1.73m^2	91 (20)	91 (20)	0.8	93 (19)	89 (19)	0.002
GFR** ml/min/1.73m^2	86 (23)	86 (22)	0.9	88 (21)	83 (19)	0.002
HDL cholesterol mmol/l	1.7 (0.3)	1.7 (0.4)	0.7	1.7 (0.4)	1.7 (0.4)	0.2
Total cholesterol mmol/l	4.8 (1.0)	4.7 (1.0)	0.5	5.0 (1.0)	4.8 (0.91)	0.02
Never smoker	81 (64)	880 (68)		104 (60)	1136 (66)	
Ex smoker	9 (7)	88 (7)		13 (7)	149 (9)	
Current smoker	36 (29)	327 (25)	0.6	57 (33)	446 (25)	0.05

Abbreviations: HbA_{1c}, haemoglobin A_{1c}; IQR, interquartile range; SD, standard deviation; UAER, urinary albumin excretion rate; BMI, body mass index; WHR, waist hip ratio; HDL, high-density lipoprotein. *P values were calculated using Fisher's exact tests for categorical variables, two-group t-tests for continuous normally-distributed variables, or Wilcoxon rank-sum tests for continuous left-skewed variables.

GFR* CKD-EPI Levey AS, Stevens LA, Schmid CH. Ann Int Med 2009; 150; 604-12

GFR** MDRD4 Levey AS, Coresh J, Greene T Clin Chem 2007; 53; 766-72

eGDR*** estimated glucose disposal rate. From Williams KV, Erbey JR, Becker D. Diabetes 2000; 49; 626-32

Supplementary Table 2.
Endogenous miRNA expression in different endothelial cell types.

QPCR analysis demonstrated comparable levels of endogenous miRNA expression, miR-27b, miR-126-3p, miR-126-5p (miR-126*) and miR-320a among four different endothelial cells: human retinal endothelial cells (HRECs), human saphenous vein endothelial cells (HSaVEC), human aortic endothelial cells (HAoEC) and human umbilical vein endothelial cells (HUVECs). Note that miR-320a is consistently more abundant than miR-27b.

Cell Type	MiRNAs Ct Mean, (SD)			
	miR-27b	**miR-126-3p**	**miR-126-5p**	**miR-320a**
HREC	30.08 (0.36)	17.98 (0.01)	23.15 (0.03)	25.29 (0.04)
HSaVEC	29.9 (0.53)	17.16 (0.28)	20.67 (0.85)	23.26 (0.34)
HAoEC	29.86 (0.26)	17.34 (0.35)	20.63 (0.41)	23.15 (0.19)
HUVEC	29.87 (0.38)	17.07 (0.12)	20.61 (0.28)	22.92 (0.19)

Abbreviations: Ct, cycle threshold; SD, standard deviation; HREC, human retinal endothelial cells; HSaVEC, human saphenous vein endothelial cells; HAoEC, human aortic endothelial cells; HUVEC, human umbilical vein endothelial cells.

Supplementary Table 3.
Mass spectrometry spectral counts for proteins identified in conditioned media of transfected endothelial cells (n=4)

			Mimic Control (Mc)				Mimic for miR-27b						Mimic for miR-320a					
Identified Proteins (668)	**Accession Number**	**Molecular Weight**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**Fold**	**P-value**	**1**	**2**	**3**	**4**	**Fold**	**P-value**
Serum albumin	ALBU_BOVIN	69 kDa	1160.7	866.3	699.2	303.0	1071.9	1115.3	251.4	512.5	1.0	0.946	1226.2	501.2	1331.4	481.5	1.2	0.676
Serotransferrin	TRFE_BOVIN	78 kDa	224.9	207.7	174.4	69.9	313.9	249.8	57.0	104.7	1.1	0.869	275.1	110.9	320.4	105.4	1.2	0.628
Alpha-2-HS-glycoprotein	FETUA_BOVIN	38 kDa	181.4	134.7	120.5	69.1	173.6	180.9	58.0	99.8	1.0	0.966	208.0	99.5	246.8	108.8	1.3	0.404
Alpha-2-macroglobulin	A2MG_BOVIN	168 kDa	172.3	143.8	115.6	50.7	181.9	167.9	34.8	59.1	0.9	0.840	201.2	88.9	202.7	80.5	1.2	0.616
Actin, cytoplasmic type 5	ACT5_CHICK (+8)	42 kDa	119.7	116.4	140.5	120.6	59.3	120.6	111.7	194.6	1.0	0.929	105.4	143.5	79.3	131.2	0.9	0.571
Alpha-1-antiproteinase	A1AT_BOVIN	46 kDa	152.3	108.4	100.5	32.4	189.1	152.2	35.9	51.7	1.1	0.852	173.8	67.6	182.3	63.1	1.2	0.592
Vimentin	VIME_HUMAN	54 kDa	74.4	74.2	73.3	89.0	27.2	73.2	67.8	141.7	1.0	0.993	37.0	75.2	32.8	88.0	0.7	0.255
Alpha-fetoprotein	FETA_BOVIN	69 kDa	76.2	71.9	70.8	14.7	129.8	96.2	22.1	27.1	1.2	0.746	105.4	38.7	129.1	31.5	1.3	0.558
Heat shock cognate 71 kDa protein	HSP7C_BOVIN (+1)	71 kDa	27.2	42.2	46.6	49.3	7.8	51.7	65.3	57.9	1.1	0.771	34.2	53.9	18.1	45.7	0.9	0.730
Fetuin-B	FETUB_BOVIN	43 kDa	45.3	65.1	40.0	14.7	56.6	66.0	13.1	17.2	0.9	0.864	93.1	28.9	82.6	24.9	1.4	0.470
Hemoglobin fetal subunit beta	HBBF_BOVIN	16 kDa	61.7	55.9	42.4	26.5	52.7	56.0	20.0	51.7	1.0	0.899	61.6	33.4	60.0	39.0	1.0	0.864
Filamin-A	FLNA_HUMAN	281 kDa	1.8	36.5	46.0	71.3	3.9	35.9	66.0	71.4	1.1	0.808	20.5	57.0	12.5	60.6	1.0	0.948
Tubulin beta-5 chain	TBB5_BOVIN (+1)	50 kDa	10.9	39.9	47.8	52.2	10.0	38.8	43.2	51.7	1.0	0.894	28.7	44.0	18.1	48.1	0.9	0.808
Apolipoprotein A-I	APOA1_BOVIN	30 kDa	78.0	34.2	45.4	11.0	70.4	34.5	21.8	28.3	0.9	0.853	46.5	26.6	61.1	26.6	1.0	0.909
Filamin-B	FLNB_HUMAN	278 kDa	1.8	25.1	37.5	64.0	2.8	24.4	68.2	54.2	1.2	0.797	6.8	51.6	4.5	38.2	0.8	0.710
Complement C3	CO3_BOVIN	187 kDa	18.1	42.2	28.5	14.7	74.9	37.3	8.0	6.2	1.2	0.758	52.0	13.7	55.5	13.3	1.3	0.586
Vitamin D-binding protein	VTDB_BOVIN	53 kDa	50.8	38.8	32.1	9.6	57.1	47.4	10.9	11.1	1.0	0.939	49.3	25.8	62.3	23.2	1.2	0.587
Putative elongation factor 1-alpha-like 3	EF1A3_HUMAN (+2)	50 kDa	32.6	35.4	47.8	30.9	12.2	41.6	37.4	51.7	1.0	0.923	38.3	35.7	29.4	35.7	0.9	0.678

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Glyceraldehyde-3-phosphate dehydrogenase	G3P_HUMAN	36 kDa	16.3	25.1	33.9	37.5	8.9	18.7	29.7	53.0	1.0	0.954	16.4	28.9	14.7	43.2	0.9	0.777
Fibronectin	FINC_BOVIN	272 kDa	23.6	26.3	10.9	25.0	22.7	24.4	27.2	34.5	1.3	0.241	21.9	21.3	11.3	36.5	1.1	0.842
Hemoglobin subunit alpha	HBA_BOVIN	15 kDa	50.8	29.7	30.9	11.0	44.4	18.7	21.0	24.6	0.9	0.746	23.3	28.9	34.0	26.6	0.9	0.790
Annexin A2	ANXA2_HUMAN	39 kDa	41.7	24.0	29.7	20.6	12.8	20.1	29.7	43.1	0.9	0.762	19.2	34.2	15.9	34.0	0.9	0.652
Tubulin alpha-1C chain	TBA1C_CRIGR	50 kDa	5.4	18.3	40.6	22.8	10.0	14.4	38.1	34.5	1.1	0.816	13.7	34.9	12.5	33.2	1.1	0.855
Elongation factor 2	EF2_HUMAN (+1)	95 kDa	0.0	24.0	29.7	46.3	1.7	5.7	33.4	43.1	0.8	0.784	4.1	35.7	4.5	34.9	0.8	0.706
Alpha-enolase	ENOA_HUMAN (+1)	47 kDa	10.9	29.7	33.3	28.7	10.0	27.3	26.8	43.1	1.0	0.894	21.9	29.6	17.0	31.5	1.0	0.922
Moesin	MOES_HUMAN	68 kDa	1.8	20.5	23.6	36.0	4.4	21.5	35.9	44.3	1.3	0.610	4.1	36.5	6.8	27.4	0.9	0.870
Pyruvate kinase PKM	KPYM_HUMAN	58 kDa	3.6	18.3	31.5	35.3	5.0	7.2	34.1	45.6	1.0	0.951	8.2	30.4	4.5	29.9	0.8	0.708
Kininogen-1	KNG1_BOVIN	69 kDa	25.4	32.0	18.2	7.4	35.5	31.6	5.4	6.2	0.9	0.917	38.3	15.9	46.4	14.1	1.4	0.444
Heat shock protein HSP 90-beta	HS90B_HUMAN (+3)	83 kDa	0.0	4.6	13.9	46.3	0.6	2.9	33.7	56.7	1.4	0.685	5.5	22.8	6.8	43.2	1.2	0.815
Alpha-1B-glycoprotein	A1BG_BOVIN	54 kDa	38.1	29.7	27.8	9.6	36.0	30.1	7.3	6.2	0.8	0.539	34.2	15.2	38.5	13.3	1.0	0.914
Serpin A3-2	SPA32_BOVIN	46 kDa	30.8	18.3	20.6	3.7	42.7	21.5	5.8	7.4	1.1	0.924	27.4	11.4	29.4	10.0	1.1	0.880
Peroxiredoxin-1	PRDX1_HUMAN	22 kDa	0.0	29.7	21.2	28.7	3.9	18.7	25.8	39.4	1.1	0.846	19.2	29.6	7.9	25.7	1.0	0.934
Plasminogen	PLMN_BOVIN	91 kDa	9.1	24.0	16.3	5.9	37.7	28.7	2.5	2.5	1.3	0.704	32.8	8.4	36.2	8.3	1.6	0.420
Basement membrane-specific heparan sulfate proteoglycan core protein	**PGBM_HUMAN**	**469 kDa**	**16.3**	**16.0**	**32.1**	**30.9**	12.2	10.0	8.7	22.2	0.6	0.104	**8.2**	**7.6**	**7.9**	**15.8**	**0.4**	**0.044**
Myosin-9	MYH9_HUMAN	227 kDa	0.0	4.6	11.5	48.5	0.0	1.4	44.6	48.0	1.5	0.684	0.0	25.1	2.3	23.2	0.8	0.797
78 kDa glucose-regulated protein	GRP78_HUMAN	72 kDa	14.5	5.7	20.6	17.6	8.9	4.3	22.9	38.2	1.3	0.659	12.3	37.2	10.2	31.5	1.6	0.332
Alpha-1-acid glycoprotein	A1AG_BOVIN	23 kDa	32.6	8.0	24.2	1.5	42.7	15.8	8.7	2.5	1.1	0.944	23.3	12.9	37.4	8.3	1.2	0.702

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
EGF-containing fibulin-like extracellular matrix protein 1	**FBLN3_HUMAN (+1)**	**55 kDa**	**32.6**	**27.4**	**19.4**	**23.5**	**6.1**	**14.4**	**9.8**	**16.0**	**0.4**	**0.009**	15.1	23.5	17.0	14.9	0.7	0.063
Neuroblast differentiation-associated protein AHNAK	AHNK_HUMAN	629 kDa	1.8	8.0	9.1	50.7	0.6	10.0	26.5	12.3	0.7	0.704	2.7	16.7	0.0	10.8	0.4	0.457
Protein disulfide-isomerase A3	PDIA3_HUMAN (+1)	57 kDa	23.6	16.0	12.7	19.1	6.1	18.7	13.8	32.0	1.0	0.974	15.1	31.9	11.3	25.7	1.2	0.580
Peptidyl-prolyl cis-trans isomerase A	PPIA_CHLAE	18 kDa	3.6	3.4	20.0	12.5	8.3	11.5	37.7	19.7	2.0	0.276	4.1	22.8	3.4	16.6	1.2	0.777
Galectin-1	LEG1_HUMAN	15 kDa	12.7	25.1	13.9	21.3	5.5	27.3	14.5	28.3	1.0	0.921	17.8	16.7	13.6	18.3	0.9	0.625
Heterogeneous nuclear ribonucleoproteins A2/B1	ROA2_HUMAN (+3)	37 kDa	1.8	8.0	17.0	23.5	0.6	8.6	22.1	24.6	1.1	0.856	6.8	26.6	2.3	17.4	1.1	0.925
L-lactate dehydrogenase A chain	LDHA_HUMAN	37 kDa	1.8	12.6	18.2	16.9	1.1	10.0	16.7	25.9	1.1	0.874	6.8	23.5	4.5	24.9	1.2	0.707
Hemopexin	HEMO_BOVIN	52 kDa	5.4	11.4	13.9	4.4	36.6	14.4	2.2	1.2	1.5	0.609	16.4	3.8	29.4	5.0	1.6	0.492
Alpha-actinin-1	ACTN1_HUMAN	103 kDa	0.0	5.7	27.2	20.6	3.3	4.3	35.6	22.2	1.2	0.778	0.0	19.7	0.0	14.9	0.6	0.584
Cofilin-1	COF1_HUMAN	19 kDa	7.3	17.1	17.6	19.9	3.9	23.0	13.1	24.6	1.0	0.906	15.1	18.2	6.8	18.3	0.9	0.832
14-3-3 protein epsilon	1433E_BOVIN	29 kDa	1.8	12.6	23.0	19.1	3.9	10.0	21.4	13.6	0.9	0.759	9.6	15.2	4.5	11.6	0.7	0.488
L-lactate dehydrogenase B chain	LDHB_HUMAN	37 kDa	3.6	21.7	16.3	25.7	1.7	21.5	14.9	25.9	0.9	0.908	13.7	21.3	9.1	22.4	1.0	0.968
Alpha-2-antiplasmin	A2AP_BOVIN	55 kDa	10.9	16.0	6.7	4.4	18.3	17.2	2.5	4.9	1.1	0.803	17.8	6.8	19.2	7.5	1.4	0.453
Thrombospondin-1	**TSP1_HUMAN**	**129 kDa**	**12.7**	**12.6**	**14.5**	**16.2**	**11.6**	**10.0**	**6.2**	**8.6**	**0.7**	**0.017**	**10.9**	**7.6**	**9.1**	**10.0**	**0.7**	**0.007**
Plasminogen activator inhibitor 1	PAI1_HUMAN	45 kDa	16.3	6.8	12.7	5.9	10.0	7.2	9.8	7.4	0.8	0.518	5.5	9.9	5.7	5.8	0.6	0.236
Eukaryotic initiation factor 4A-I	IF4A1_BOVIN (+1)	46 kDa	1.8	9.1	15.7	12.5	1.1	7.2	22.5	17.2	1.2	0.713	5.5	15.2	2.3	16.6	1.0	0.986
Tropomyosin alpha-3 chain	TPM3_RAT	29 kDa	9.1	10.3	10.9	14.0	2.2	17.2	17.1	14.8	1.2	0.663	13.7	12.9	7.9	12.5	1.1	0.693
Heterogeneous nuclear ribonucleoprotein K	HNRPK_HUMAN (+2)	51 kDa	5.4	14.8	12.7	27.2	0.6	14.4	12.7	17.2	0.7	0.536	12.3	12.9	4.5	14.9	0.7	0.483

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Profilin-1	PROF1_HUMAN	15 kDa	5.4	11.4	13.9	9.6	8.3	11.5	20.0	11.1	1.3	0.431	10.9	11.4	6.8	10.0	1.0	0.887
Protein disulfide-isomerase	PDIA1_HUMAN (+1)	57 kDa	3.6	4.6	8.5	9.6	1.7	4.3	11.6	12.3	1.1	0.774	1.4	24.3	4.5	10.0	1.5	0.550
Triosephosphate isomerase	TPIS_HUMAN (+1)	31 kDa	3.6	9.1	18.2	7.4	1.7	7.2	19.6	13.6	1.1	0.858	1.4	15.2	1.1	19.1	1.0	0.949
Protein AMBP	AMBP_BOVIN	39 kDa	9.1	12.6	9.7	3.7	18.9	12.9	4.4	2.5	1.1	0.841	16.4	10.6	14.7	8.3	1.4	0.201
Annexin A1	ANXA1_HUMAN	39 kDa	3.6	8.0	7.9	11.0	4.4	7.2	13.4	12.3	1.2	0.540	5.5	13.7	3.4	11.6	1.1	0.764
A-kinase anchor protein 12	AKA12_HUMAN	191 kDa	0.0	5.7	2.4	31.6	0.0	4.3	9.1	11.1	0.6	0.649	4.1	15.2	3.4	14.1	0.9	0.931
Fructose-bisphosphate aldolase A	ALDOA_HUMAN	39 kDa	0.0	8.0	12.7	12.5	2.2	10.0	11.2	14.8	1.2	0.760	5.5	8.4	4.5	8.3	0.8	0.631
Transketolase	TKT_HUMAN	68 kDa	0.0	3.4	13.3	14.7	0.0	4.3	14.9	16.0	1.1	0.867	1.4	12.9	2.3	14.9	1.0	0.999
Clathrin heavy chain 1	CLH1_HUMAN (+1)	192 kDa	0.0	3.4	8.5	18.4	0.0	2.9	18.1	14.8	1.2	0.825	2.7	10.6	0.0	14.1	0.9	0.897
40S ribosomal protein S3	RS3_BOVIN (+1)	27 kDa	0.0	2.3	6.7	17.6	1.1	2.9	10.9	20.9	1.3	0.714	1.4	8.4	1.1	19.1	1.1	0.889
Transgelin-2	TAGL2_HUMAN (+1)	22 kDa	0.0	6.8	9.7	17.6	1.1	2.9	16.7	4.9	0.7	0.687	1.4	10.6	2.3	9.1	0.7	0.562
Phosphoglycerate kinase 1	PGK1_HUMAN (+1)	45 kDa	0.0	2.3	18.2	9.6	1.7	2.9	22.5	7.4	1.1	0.867	2.7	8.4	0.0	7.5	0.6	0.561
Myosin light polypeptide 6	MYL6_BOVIN (+1)	17 kDa	0.0	6.8	8.5	18.4	1.1	4.3	11.2	23.4	1.2	0.808	4.1	11.4	2.3	11.6	0.9	0.820
Inter-alpha-trypsin inhibitor heavy chain H4	ITIH4_BOVIN	102 kDa	3.6	4.6	9.1	0.0	25.0	1.4	1.8	0.0	1.6	0.688	4.1	3.8	11.3	0.8	1.2	0.819
Thioredoxin domain-containing protein 5	TXND5_HUMAN	48 kDa	14.5	5.7	12.7	4.4	6.1	8.6	7.3	8.6	0.8	0.556	5.5	13.7	5.7	12.5	1.0	0.995
Antithrombin-III	ANT3_BOVIN	52 kDa	5.4	9.1	6.7	2.2	18.3	8.6	1.8	3.7	1.4	0.602	10.9	5.3	12.5	5.0	1.4	0.329
Nucleoside diphosphate kinase B	NDKB_MOUSE (+1)	17 kDa	0.0	9.1	9.1	14.0	0.6	8.6	11.2	11.1	1.0	0.966	8.2	12.9	5.7	7.5	1.1	0.882
Talin-1	TLN1_HUMAN	270 kDa	0.0	4.6	5.4	20.6	0.0	8.6	17.4	12.3	1.3	0.750	2.7	6.1	1.1	10.8	0.7	0.643
Calreticulin	CALR_HUMAN (+1)	48 kDa	0.0	3.4	7.3	10.3	0.6	2.9	7.3	13.6	1.2	0.831	2.7	12.9	5.7	13.3	1.6	0.365
Beta-2-glycoprotein 1	APOH_BOVIN	38 kDa	5.4	1.1	16.3	0.0	21.6	2.9	3.3	0.0	1.2	0.852	8.2	6.1	19.2	1.7	1.5	0.583

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Transitional endoplasmic reticulum ATPase	TERA_HUMAN (+1)	89 kDa	0.0	2.3	12.1	8.8	0.0	0.0	21.0	13.6	1.5	0.653	0.0	14.4	0.0	9.1	1.0	0.985
SPARC	SPRC_BOVIN	35 kDa	7.3	1.1	11.5	0.0	6.1	0.0	5.8	7.4	1.0	0.964	1.4	9.9	0.0	1.7	0.6	0.636
Fascin	FSCN1_HUMAN	55 kDa	1.8	6.8	10.3	11.8	0.0	10.0	13.4	16.0	1.3	0.620	4.1	10.6	4.5	10.8	1.0	0.956
40S ribosomal protein SA	RSSA_CHICK (+2)	33 kDa	3.6	8.0	7.9	9.6	2.2	5.7	10.5	13.6	1.1	0.803	4.1	9.9	4.5	12.5	1.1	0.850
Vinculin	VINC_HUMAN	124 kDa	0.0	6.8	6.1	13.2	0.0	4.3	15.6	12.3	1.2	0.747	1.4	9.1	0.0	10.0	0.8	0.716
14-3-3 protein zeta/delta	1433Z_BOVIN	28 kDa	5.4	16.0	20.6	18.4	3.3	17.2	18.5	19.7	1.0	0.939	6.8	16.7	5.7	14.9	0.7	0.390
Complement factor B	CFAB_BOVIN	85 kDa	5.4	11.4	6.7	3.7	18.3	11.5	1.8	2.5	1.3	0.708	10.9	3.8	12.5	5.8	1.2	0.602
Peroxiredoxin-6	PRDX6_HUMAN (+1)	25 kDa	1.8	4.6	6.7	9.6	0.6	4.3	8.3	11.1	1.1	0.886	4.1	9.1	1.1	9.1	1.0	0.934
Myristoylated alanine-rich C-kinase substrate	MARCS_HUMAN	32 kDa	9.1	12.6	6.1	8.8	1.1	11.5	4.0	9.9	0.7	0.410	8.2	9.9	5.7	7.5	0.9	0.443
Chloride intracellular channel protein 1	CLIC1_HUMAN	27 kDa	1.8	8.0	10.9	9.6	0.0	5.7	11.2	14.8	1.0	0.925	5.5	9.1	2.3	8.3	0.8	0.634
Connective tissue growth factor	CTGF_HUMAN	38 kDa	10.9	5.7	7.9	5.1	3.9	2.9	5.1	6.2	0.6	0.112	2.7	5.3	3.4	3.3	0.5	0.058
Adenylyl cyclase-associated protein 1	CAP1_HUMAN	52 kDa	0.0	4.6	6.1	7.4	0.0	4.3	11.2	9.9	1.4	0.569	4.1	9.1	2.3	6.6	1.2	0.652
Inter-alpha-trypsin inhibitor heavy chain H2	ITIH2_MOUSE	106 kDa	7.3	8.0	7.3	0.7	11.6	7.2	2.2	1.2	1.0	0.935	12.3	6.8	13.6	2.5	1.5	0.373
Peptidyl-prolyl cis-trans isomerase FKBP1A	FKB1A_HUMAN (+2)	12 kDa	5.4	5.7	7.9	11.0	1.7	5.7	13.8	12.3	1.1	0.795	4.1	7.6	3.4	7.5	0.8	0.314
Ubiquitin-40S ribosomal protein S27a	RS27A_BOVIN	18 kDa	3.6	5.7	6.1	5.9	0.6	5.7	7.3	9.9	1.1	0.808	2.7	9.1	1.1	4.2	0.8	0.602
Serum albumin	ALBU_HUMAN	69 kDa	110.6	87.9	54.5	29.4	69.3	90.4	17.4	60.4	0.8	0.652	101.3	37.2	106.4	40.7	1.0	0.977
Elongation factor 1-gamma	EF1G_HUMAN	50 kDa	0.0	5.7	7.9	11.8	0.0	10.0	12.7	11.1	1.3	0.595	6.8	7.6	0.0	8.3	0.9	0.842
Tropomyosin alpha-4 chain	TPM4_HUMAN (+1)	29 kDa	7.3	10.3	6.7	12.5	1.1	15.8	15.6	18.5	1.4	0.443	9.6	15.9	4.5	14.9	1.2	0.519
10 kDa heat shock protein, mitochondrial	CH10_BOVIN	11 kDa	10.9	1.1	2.4	4.4	0.6	2.9	4.0	8.6	0.9	0.807	1.4	7.6	0.0	10.0	1.0	0.996
Heterogeneous nuclear ribonucleoprotein A1	ROA1_BOVIN (+1)	34 kDa	0.0	4.6	13.9	11.8	0.0	2.9	15.6	7.4	0.9	0.822	2.7	9.9	1.1	6.6	0.7	0.542

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Caldesmon	CALD1_HUMAN	93 kDa	0.0	3.4	5.4	14.0	0.0	1.4	8.0	8.6	0.8	0.758	2.7	10.6	3.4	9.1	1.1	0.839
Transaldolase	TALDO_HUMAN	38 kDa	0.0	5.7	7.9	5.1	0.0	1.4	8.7	7.4	0.9	0.917	1.4	7.6	0.0	5.8	0.8	0.701
Heat shock protein HSP 90-alpha	HS90A_HUMAN (+5)	85 kDa	0.0	0.0	8.5	35.3	0.0	0.0	25.0	43.1	1.6	0.667	0.0	15.9	6.8	33.2	1.3	0.792
Protein-glutamine gamma-glutamyltransferase 2	TGM2_HUMAN	77 kDa	0.0	4.6	6.1	11.8	0.0	2.9	5.1	4.9	0.6	0.425	4.1	6.1	3.4	5.0	0.8	0.725
Spectrin alpha chain, non-erythrocytic 1	SPTN1_HUMAN	285 kDa	0.0	4.6	0.0	21.3	0.0	1.4	12.0	7.4	0.8	0.835	0.0	4.6	0.0	9.1	0.5	0.609
Lactotransferrin	TRFL_HUMAN	78 kDa	0.0	0.0	0.0	0.0	0.0	15.8	52.6	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
40S ribosomal protein S20	RS20_BOVIN (+2)	13 kDa	0.0	4.6	1.8	11.8	0.0	5.7	5.8	13.6	1.4	0.663	4.1	7.6	3.4	10.8	1.4	0.559
Alpha-actinin-4	ACTN4_HUMAN (+1)	105 kDa	0.0	6.8	27.2	22.8	0.0	4.3	33.7	24.6	1.1	0.893	0.0	22.8	0.0	14.1	0.6	0.581
Pentraxin-related protein PTX3	PTX3_HUMAN	42 kDa	9.1	2.3	8.5	1.5	6.7	0.0	4.7	2.5	0.6	0.480	4.1	10.6	1.1	7.5	1.1	0.865
Guanine nucleotide-binding protein subunit beta-2-like 1	GBLP_BOVIN	35 kDa	3.6	2.3	6.7	5.9	1.7	2.9	12.7	7.4	1.3	0.599	2.7	6.1	1.1	10.8	1.1	0.820
Apolipoprotein A-II	APOA2_BOVIN	11 kDa	10.9	3.4	3.0	2.9	7.8	4.3	3.3	6.2	1.1	0.895	4.1	4.6	2.3	4.2	0.7	0.558
Filamin-C	FLNC_HUMAN	291 kDa	0.0	4.6	6.1	16.9	0.0	4.3	17.8	7.4	1.1	0.929	0.0	10.6	1.1	10.0	0.8	0.762
Endothelial protein C receptor	EPCR_HUMAN	27 kDa	16.3	0.0	7.3	1.5	5.5	0.0	4.4	6.2	0.6	0.601	5.5	3.0	2.3	5.0	0.6	0.579
Keratin, type II cytoskeletal 1	K2C1_HUMAN	66 kDa	0.0	0.0	1.8	1.5	2.2	4.3	13.1	2.5	6.7	0.163	0.0	0.0	1.1	1.7	0.8	0.852
40S ribosomal protein S16	RS16_BOVIN	16 kDa	0.0	1.1	3.0	11.8	0.0	0.0	9.4	16.0	1.6	0.636	0.0	3.0	0.0	10.8	0.9	0.891
Synaptic vesicle membrane protein VAT-1 homolog	VAT1_HUMAN	42 kDa	1.8	3.4	4.8	7.4	0.0	2.9	10.5	7.4	1.2	0.763	1.4	6.1	0.0	5.0	0.7	0.527
14-3-3 protein theta	1433T_BOVIN	28 kDa	3.6	12.6	18.8	16.9	2.8	14.4	15.6	16.0	0.9	0.872	10.9	15.2	4.5	12.5	0.8	0.613
Adenosylhomocysteinase	SAHH_HUMAN	48 kDa	0.0	4.6	6.7	10.3	0.0	5.7	8.3	6.2	0.9	0.913	4.1	8.4	1.1	7.5	1.0	0.968
Inter-alpha-trypsin inhibitor heavy chain H3	ITIH3_BOVIN	100 kDa	3.6	8.0	4.8	3.7	11.1	7.2	1.8	0.0	1.0	0.996	8.2	3.0	12.5	3.3	1.3	0.521

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Plastin-3	PLST_HUMAN	71 kDa	0.0	0.0	4.8	6.6	0.0	0.0	20.7	4.9	2.2	0.535	0.0	1.5	0.0	1.7	0.3	0.313
Thymosin beta-12	TYB12_LATJA (+5)	5 kDa	3.6	10.3	4.8	5.9	1.7	11.5	2.5	7.4	0.9	0.892	8.2	6.1	6.8	9.1	1.2	0.430
Endoplasmin	ENPL_HUMAN	92 kDa	0.0	2.3	1.8	8.8	0.6	2.9	6.2	17.2	2.1	0.446	1.4	13.7	2.3	10.8	2.2	0.343
Cytoplasmic dynein 1 heavy chain 1	DYHC1_HUMAN	532 kDa	0.0	0.0	0.6	19.1	0.0	0.0	6.9	2.5	0.5	0.634	0.0	0.8	0.0	8.3	0.5	0.631
Serum albumin	ALBU_EQUAS	69 kDa	70.7	57.1	30.3	21.3	41.0	66.0	13.1	29.6	0.8	0.659	78.0	23.5	57.7	28.2	1.0	0.910
Gelsolin	GELS_BOVIN	81 kDa	1.8	5.7	3.6	2.2	11.1	7.2	1.5	1.2	1.6	0.499	2.7	3.0	9.1	3.3	1.4	0.525
Keratin, type I cytoskeletal 10	K1C10_HUMAN	59 kDa	9.1	1.1	0.0	0.7	2.2	8.6	10.5	3.7	2.3	0.270	2.7	1.5	1.1	2.5	0.7	0.745
Proliferation-associated protein 2G4	PA2G4_HUMAN	44 kDa	0.0	4.6	2.4	8.1	0.0	4.3	8.0	7.4	1.3	0.662	2.7	4.6	2.3	6.6	1.1	0.893
Tubulin beta-6 chain	TBB6_HUMAN	50 kDa	0.0	16.0	18.2	17.6	0.0	12.9	22.5	27.1	1.2	0.731	6.8	22.0	4.5	14.1	0.9	0.861
Heterogeneous nuclear ribonucleoprotein D-like	HNRDL_HUMAN	46 kDa	0.0	3.4	4.8	6.6	0.0	0.0	6.9	3.7	0.7	0.639	1.4	6.8	0.0	6.6	1.0	0.997
WD repeat-containing protein 1	WDR1_HUMAN	66 kDa	0.0	1.1	9.1	3.7	0.0	0.0	14.1	6.2	1.5	0.700	0.0	4.6	0.0	3.3	0.6	0.548
Cysteine and glycine-rich protein 1	CSRP1_HUMAN (+2)	21 kDa	0.0	3.4	6.7	11.0	0.6	1.4	8.7	7.4	0.9	0.817	0.0	6.1	0.0	6.6	0.6	0.510
T-complex protein 1 subunit theta	TCPQ_HUMAN	60 kDa	0.0	4.6	4.8	11.0	0.0	4.3	8.3	7.4	1.0	0.974	2.7	6.1	2.3	9.1	1.0	0.984
Microtubule-associated protein 4	MAP4_HUMAN	121 kDa	0.0	4.6	1.2	14.7	0.0	2.9	7.3	6.2	0.8	0.791	0.0	5.3	0.0	8.3	0.7	0.680
Phosphoglycerate mutase 1	PGAM1_HUMAN (+1)	29 kDa	0.0	4.6	4.2	6.6	0.6	1.4	9.4	4.9	1.1	0.928	0.0	4.6	0.0	6.6	0.7	0.645
Beta-actin-like protein 2	ACTBL_MOUSE	42 kDa	23.6	24.0	59.3	25.7	17.7	0.0	48.6	55.4	0.9	0.870	19.2	41.8	15.9	34.0	0.8	0.630
40S ribosomal protein S12	RS12_BOVIN (+3)	15 kDa	0.0	3.4	1.8	5.1	0.0	0.0	5.8	9.9	1.5	0.643	0.0	6.1	0.0	8.3	1.4	0.696
Insulin-like growth factor-binding protein 7	IBP7_HUMAN	29 kDa	7.3	3.4	3.6	3.7	1.7	5.7	4.7	4.9	0.9	0.861	1.4	7.6	4.5	5.0	1.0	0.941
Complement C4 (Fragments)	CO4_BOVIN	102 kDa	3.6	3.4	3.0	1.5	13.3	8.6	0.7	2.5	2.2	0.327	4.1	3.0	5.7	1.7	1.3	0.490
Brain acid soluble protein 1	BASP1_HUMAN	23 kDa	5.4	5.7	4.2	6.6	1.1	5.7	2.5	6.2	0.7	0.291	5.5	6.8	2.3	7.5	1.0	0.994

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Purine nucleoside phosphorylase	PNPH_HUMAN	32 kDa	0.0	0.0	6.7	1.5	1.1	0.0	15.6	2.5	2.4	0.524	0.0	2.3	0.0	2.5	0.6	0.651
Trypsin	TRYP_PIG	24 kDa	14.5	6.8	3.6	1.5	3.3	8.6	1.5	3.7	0.6	0.504	8.2	1.5	6.8	2.5	0.7	0.597
Collagen alpha-1(I) chain	CO1A1_BOVIN	139 kDa	5.4	6.8	0.6	2.9	1.7	12.9	4.7	0.0	1.2	0.798	4.1	4.6	4.5	5.0	1.1	0.702
Aminopeptidase N	AMPN_HUMAN	110 kDa	3.6	2.3	3.6	6.6	0.0	2.9	7.3	2.5	0.8	0.635	1.4	3.8	1.1	5.0	0.7	0.388
60S ribosomal protein L7	RL7_HUMAN	29 kDa	0.0	0.0	0.0	11.0	0.0	0.0	2.9	8.6	1.0	0.972	0.0	0.8	0.0	9.1	0.9	0.939
Heterogeneous nuclear ribonucleoprotein H	HNRH1_HUMAN (+1)	49 kDa	0.0	6.8	4.8	9.6	0.0	1.4	6.2	4.9	0.6	0.417	2.7	4.6	3.4	6.6	0.8	0.678
Peptidyl-prolyl cis-trans isomerase B	PPIB_HUMAN	24 kDa	1.8	0.0	4.2	2.9	2.2	0.0	6.2	6.2	1.6	0.470	0.0	8.4	1.1	6.6	1.8	0.468
Serpin A3-7	SPA37_BOVIN	47 kDa	14.5	8.0	9.1	0.0	13.9	11.5	3.3	3.7	1.0	0.965	13.7	6.8	13.6	5.8	1.3	0.593
Actin-related protein 3	ARP3_BOVIN	47 kDa	0.0	3.4	4.2	11.0	0.0	4.3	7.3	3.7	0.8	0.767	1.4	6.1	0.0	5.8	0.7	0.644
Nuclease-sensitive element-binding protein 1	YBOX1_BOVIN (+1)	36 kDa	3.6	3.4	0.6	5.9	0.0	4.3	2.5	4.9	0.9	0.785	1.4	3.0	2.3	4.2	0.8	0.607
Cathepsin B	CATB_HUMAN	38 kDa	3.6	4.6	4.2	6.6	1.1	4.3	3.6	3.7	0.7	0.152	1.4	8.4	1.1	5.0	0.8	0.684
GTP-binding nuclear protein Ran	RAN_BOVIN (+6)	24 kDa	0.0	4.6	6.1	6.6	0.0	1.4	5.1	9.9	0.9	0.938	0.0	5.3	0.0	6.6	0.7	0.588
Rab GDP dissociation inhibitor beta	GDIB_HUMAN	51 kDa	0.0	1.1	3.0	10.3	0.0	0.0	9.1	1.2	0.7	0.755	1.4	3.8	0.0	1.7	0.5	0.481
Angiotensinogen	ANGT_SHEEP	51 kDa	0.0	3.4	3.0	2.2	10.0	1.4	1.5	0.0	1.5	0.686	5.5	0.8	9.1	0.8	1.9	0.436
Calmodulin-alpha (Fragment)	CALMA_ARBPU (+7)	16 kDa	3.6	4.6	4.8	2.9	1.1	4.3	6.9	7.4	1.2	0.574	2.7	3.8	2.3	4.2	0.8	0.269
Splicing factor, proline- and glutamine-rich	SFPQ_HUMAN	76 kDa	3.6	2.3	1.8	4.4	0.6	2.9	2.5	3.7	0.8	0.515	2.7	6.1	0.0	5.8	1.2	0.710
Polyadenylate-binding protein 1	PABP1_RAT	71 kDa	0.0	1.1	4.8	3.7	0.0	1.4	10.5	2.5	1.5	0.671	0.0	6.8	0.0	3.3	1.1	0.952
40S ribosomal protein S21	RS21_BOVIN	9 kDa	0.0	3.4	3.0	7.4	0.0	1.4	4.4	7.4	1.0	0.946	4.1	4.6	2.3	3.3	1.0	0.948
Plasminogen activator inhibitor 1 RNA-binding protein	PAIRB_HUMAN	45 kDa	0.0	1.1	1.8	10.3	0.0	0.0	3.6	6.2	0.7	0.769	0.0	4.6	1.1	5.8	0.9	0.879

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
ATP-citrate synthase	ACLY_HUMAN	121 kDa	0.0	3.4	3.0	9.6	0.0	0.0	6.5	2.5	0.6	0.515	0.0	5.3	1.1	5.0	0.7	0.654
Staphylococcal nuclease domain-containing protein 1	SND1_HUMAN	102 kDa	0.0	2.3	2.4	7.4	0.0	0.0	8.3	6.2	1.2	0.825	0.0	3.8	0.0	7.5	0.9	0.936
Rho GDP-dissociation inhibitor 2	GDIR2_HUMAN	23 kDa	1.8	3.4	2.4	4.4	0.0	5.7	3.3	3.7	1.1	0.910	2.7	3.8	1.1	4.2	1.0	0.945
Drebrin	DREB_HUMAN	71 kDa	1.8	3.4	1.8	5.1	0.6	4.3	3.6	6.2	1.2	0.682	1.4	5.3	1.1	5.0	1.0	0.918
Malate dehydrogenase, mitochondrial	MDHM_HUMAN (+2)	36 kDa	3.6	0.0	1.8	0.7	1.1	1.4	3.3	2.5	1.3	0.597	0.0	6.1	0.0	3.3	1.5	0.651
Glutathione S-transferase omega-1	GSTO1_HUMAN	28 kDa	0.0	3.4	4.2	5.9	0.0	2.9	7.3	3.7	1.0	0.973	0.0	4.6	0.0	2.5	0.5	0.365
40S ribosomal protein S2	RS2_HUMAN (+2)	31 kDa	0.0	2.3	2.4	8.8	0.6	2.9	5.4	12.3	1.6	0.570	0.0	3.0	0.0	10.8	1.0	0.982
6-phosphogluconate dehydrogenase, decarboxylating	6PGD_HUMAN	53 kDa	0.0	2.3	5.4	5.9	0.0	0.0	7.3	4.9	0.9	0.881	0.0	5.3	0.0	4.2	0.7	0.616
Eukaryotic translation initiation factor 5A-1	IF5A1_BOVIN (+1)	17 kDa	0.0	1.1	8.5	5.1	1.1	0.0	8.7	3.7	0.9	0.913	0.0	5.3	0.0	3.3	0.6	0.540
Prelamin-A/C	LMNA_HUMAN	74 kDa	0.0	0.0	1.8	8.1	0.0	1.4	6.9	13.6	2.2	0.446	0.0	9.1	0.0	8.3	1.8	0.576
T-complex protein 1 subunit gamma	TCPG_HUMAN (+1)	61 kDa	0.0	1.1	3.0	9.6	0.0	0.0	7.6	7.4	1.1	0.920	0.0	4.6	0.0	5.8	0.8	0.761
Glutathione S-transferase P	GSTP1_HUMAN	23 kDa	0.0	1.1	8.5	5.1	1.1	2.9	7.3	4.9	1.1	0.887	1.4	5.3	0.0	4.2	0.7	0.686
Plectin	PLEC_HUMAN	532 kDa	0.0	2.3	0.0	9.6	0.0	1.4	4.0	8.6	1.2	0.858	0.0	0.8	0.0	6.6	0.6	0.705
40S ribosomal protein S18	RS18_BOVIN	18 kDa	0.0	2.3	2.4	5.1	0.6	1.4	3.6	6.2	1.2	0.779	1.4	4.6	1.1	7.5	1.5	0.549
T-complex protein 1 subunit alpha	TCPA_HUMAN (+1)	60 kDa	0.0	0.0	1.2	9.6	0.0	0.0	4.0	4.9	0.8	0.868	0.0	3.0	0.0	4.2	0.7	0.741
40S ribosomal protein S8	RS8_BOVIN	24 kDa	0.0	0.0	1.8	7.4	0.0	0.0	7.3	11.1	2.0	0.513	0.0	0.0	0.0	10.0	1.1	0.950
Pantetheinase	VNN1_BOVIN	57 kDa	1.8	4.6	3.0	1.5	6.7	5.7	0.4	2.5	1.4	0.536	6.8	1.5	6.8	2.5	1.6	0.336
High mobility group protein HMG-I/HMG-Y	HMGA1_CANFA (+2)	12 kDa	0.0	2.3	1.2	11.0	0.0	0.0	2.2	7.4	0.7	0.701	2.7	4.6	0.0	10.8	1.2	0.802
Protein disulfide-isomerase A4	PDIA4_HUMAN	73 kDa	0.0	0.0	0.6	3.7	0.0	0.0	3.3	6.2	2.2	0.490	0.0	9.1	0.0	5.0	3.3	0.360

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Serpin A3-3	SPA33_BOVIN (+1)	46 kDa	21.8	16.0	17.0	0.0	42.1	17.2	4.0	0.0	1.2	0.847	26.0	9.1	24.9	7.5	1.2	0.657
40S ribosomal protein S4, X isoform	RS4X_CHLAE (+4)	30 kDa	0.0	0.0	1.2	9.6	0.0	0.0	3.3	12.3	1.4	0.757	0.0	0.8	0.0	6.6	0.7	0.776
Putative 40S ribosomal protein S26-like 1	RS26L_HUMAN (+2)	13 kDa	0.0	0.0	0.0	9.6	0.0	0.0	1.8	6.2	0.8	0.893	0.0	0.0	1.1	7.5	0.9	0.939
T-complex protein 1 subunit eta	TCPH_HUMAN (+1)	59 kDa	0.0	0.0	2.4	6.6	0.0	0.0	6.5	1.2	0.9	0.890	0.0	3.0	0.0	3.3	0.7	0.727
Heat shock protein 105 kDa	HS105_HUMAN (+1)	97 kDa	0.0	3.4	1.8	5.9	0.0	1.4	8.0	3.7	1.2	0.825	1.4	5.3	2.3	4.2	1.2	0.760
Factor XIIa inhibitor	F12AI_BOVIN	52 kDa	0.0	4.6	1.8	0.0	13.3	4.3	0.0	0.0	2.8	0.448	4.1	0.0	5.7	0.0	1.5	0.657
40S ribosomal protein S3a	RS3A_BOVIN (+4)	30 kDa	0.0	0.0	1.2	5.1	0.0	0.0	5.1	8.6	2.2	0.486	0.0	2.3	0.0	6.6	1.4	0.759
Tubulin beta-4B chain	TBB4B_BOVIN	50 kDa	10.9	39.9	38.1	51.5	8.9	37.3	37.4	48.0	0.9	0.860	27.4	38.0	18.1	42.3	0.9	0.734
RNA-binding protein FUS	FUS_BOVIN	52 kDa	0.0	1.1	1.8	5.1	0.0	2.9	2.9	4.9	1.3	0.680	1.4	3.0	2.3	5.0	1.4	0.538
Heat shock protein beta-1	HSPB1_HUMAN	23 kDa	0.0	2.3	4.2	5.1	0.6	2.9	5.8	3.7	1.1	0.848	1.4	5.3	0.0	5.0	1.0	1.000
60S ribosomal protein L12	RL12_BOVIN (+2)	18 kDa	0.0	1.1	1.2	11.0	0.0	0.0	4.0	11.1	1.1	0.912	0.0	0.8	0.0	8.3	0.7	0.753
Stress-induced-phosphoprotein 1	STIP1_HUMAN	63 kDa	0.0	1.1	2.4	7.4	0.0	0.0	3.3	3.7	0.6	0.626	0.0	1.5	0.0	4.2	0.5	0.519
Fibronectin	FINC_HUMAN	263 kDa	10.9	9.1	9.7	14.7	9.4	5.7	16.3	16.0	1.1	0.800	6.8	12.9	6.8	17.4	1.0	0.972
26S proteasome non-ATPase regulatory subunit 2	PSMD2_HUMAN	100 kDa	0.0	1.1	0.0	8.1	0.6	2.9	4.7	3.7	1.3	0.775	4.1	4.6	4.5	5.8	2.1	0.300
T-complex protein 1 subunit delta	TCPD_HUMAN (+2)	58 kDa	0.0	2.3	2.4	7.4	0.0	0.0	3.3	7.4	0.9	0.886	0.0	3.0	0.0	3.3	0.5	0.466
40S ribosomal protein S13	RS13_BOVIN (+1)	17 kDa	0.0	1.1	1.8	10.3	0.0	0.0	4.0	6.2	0.8	0.793	0.0	0.8	0.0	5.8	0.5	0.570
Ubiquitin-like modifier-activating enzyme 1	UBA1_HUMAN	118 kDa	0.0	0.0	3.0	5.9	0.0	1.4	9.8	2.5	1.5	0.664	0.0	2.3	0.0	0.8	0.3	0.393
CD59 glycoprotein	CD59_HUMAN	14 kDa	3.6	2.3	1.2	2.9	0.6	2.9	1.5	2.5	0.7	0.388	1.4	2.3	0.0	2.5	0.6	0.247
60S ribosomal protein L30	RL30_BOVIN (+1)	13 kDa	0.0	5.7	2.4	6.6	0.6	1.4	5.1	4.9	0.8	0.734	1.4	3.0	0.0	5.8	0.7	0.587
60S ribosomal protein L6	RL6_HUMAN	33 kDa	0.0	0.0	0.0	8.8	0.0	0.0	2.5	8.6	1.3	0.852	0.0	1.5	0.0	10.0	1.3	0.845

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
60S ribosomal protein L5	RL5_HUMAN	34 kDa	0.0	0.0	2.4	9.6	0.0	0.0	4.4	4.9	0.8	0.808	0.0	2.3	0.0	5.0	0.6	0.665
60S ribosomal protein L13	RL13_HUMAN	24 kDa	0.0	0.0	0.0	8.1	0.0	0.0	3.6	7.4	1.4	0.794	0.0	0.0	0.0	5.0	0.6	0.757
Adiponectin	ADIPO_BOVIN	26 kDa	0.0	1.1	1.2	2.2	5.0	2.9	0.7	0.0	1.9	0.454	5.5	1.5	3.4	2.5	2.8	0.087
Eukaryotic translation initiation factor 2 subunit 1	IF2A_HUMAN	36 kDa	0.0	1.1	0.6	8.1	0.6	1.4	3.3	2.5	0.8	0.804	1.4	5.3	1.1	3.3	1.1	0.885
Malate dehydrogenase, cytoplasmic	MDHC_HUMAN	36 kDa	0.0	3.4	2.4	8.1	0.0	2.9	4.4	1.2	0.6	0.514	4.1	3.8	2.3	3.3	1.0	0.953
40S ribosomal protein S14	RS14_CRIGR (+1)	16 kDa	0.0	2.3	1.8	2.9	0.0	1.4	3.6	3.7	1.2	0.711	2.7	3.8	0.0	3.3	1.4	0.533
40S ribosomal protein S25	RS25_BOVIN	14 kDa	0.0	2.3	1.2	5.1	1.1	0.0	2.9	7.4	1.3	0.739	2.7	3.0	1.1	5.0	1.4	0.573
Ras GTPase-activating-like protein IQGAP1	IQGA1_HUMAN	189 kDa	0.0	1.1	0.0	2.9	0.0	2.9	8.7	1.2	3.1	0.350	0.0	0.8	0.0	0.8	0.4	0.446
Zyxin	ZYX_HUMAN	61 kDa	0.0	2.3	1.2	6.6	0.0	2.9	5.4	6.2	1.4	0.607	1.4	3.0	0.0	4.2	0.8	0.829
60S ribosomal protein L18	RL18_HUMAN (+2)	22 kDa	0.0	0.0	0.0	6.6	0.0	0.0	4.4	9.9	2.1	0.535	0.0	0.0	0.0	10.8	1.6	0.755
Histone H2A type 1-B/E	H2A1B_HUMAN (+22)	14 kDa	1.8	1.1	1.8	0.7	1.1	0.0	1.1	2.5	0.8	0.728	1.4	2.3	0.0	0.8	0.8	0.659
14-3-3 protein gamma	1433G_HUMAN (+2)	28 kDa	0.0	9.1	15.1	13.2	0.0	10.0	12.7	9.9	0.9	0.789	8.2	9.9	4.5	9.1	0.8	0.709
Macrophage migration inhibitory factor	MIF_HUMAN	12 kDa	0.0	2.3	3.6	2.9	1.1	2.9	3.3	4.9	1.4	0.484	0.0	6.8	1.1	4.2	1.4	0.660
60S ribosomal protein L27a	RL27A_HUMAN	17 kDa	0.0	0.0	0.6	5.9	0.0	0.0	3.6	9.9	2.1	0.550	0.0	0.8	0.0	5.8	1.0	0.992
Glucose-6-phosphate isomerase	G6PI_HUMAN	63 kDa	0.0	2.3	3.0	6.6	0.0	5.7	5.4	1.2	1.0	0.953	0.0	3.0	0.0	2.5	0.5	0.362
Nestin	NEST_HUMAN	177 kDa	0.0	1.1	0.0	11.8	0.0	0.0	2.9	6.2	0.7	0.778	0.0	2.3	0.0	5.8	0.6	0.722
Heat shock 70 kDa protein 4	HSP74_HUMAN (+1)	94 kDa	0.0	0.0	3.6	5.1	0.0	0.0	8.7	0.0	1.0	0.995	0.0	2.3	0.0	2.5	0.5	0.530
Protein DJ-1	PARK7_HUMAN	20 kDa	0.0	0.0	1.2	5.9	0.0	0.0	5.1	3.7	1.2	0.833	0.0	0.8	0.0	1.7	0.3	0.473
Thioredoxin	THIO_HUMAN (+1)	12 kDa	1.8	3.4	2.4	2.2	0.6	2.9	3.3	3.7	1.1	0.875	4.1	2.3	0.0	2.5	0.9	0.799
Histone H4 type VIII	H48_CHICK (+9)	11 kDa	1.8	4.6	0.6	2.2	0.0	4.3	2.2	1.2	0.8	0.775	0.0	3.0	0.0	2.5	0.6	0.459

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Septin-11	SEP11_HUMAN (+1)	49 kDa	0.0	2.3	1.2	6.6	0.0	1.4	1.5	2.5	0.5	0.482	0.0	5.3	1.1	3.3	1.0	0.965
Ubiquitin carboxyl-terminal hydrolase isozyme L1	UCHL1_HUMAN	25 kDa	0.0	2.3	1.8	5.1	0.0	2.9	3.6	2.5	1.0	0.959	1.4	1.5	1.1	4.2	0.9	0.841
F-actin-capping protein subunit alpha-1	CAZA1_HUMAN	33 kDa	0.0	2.3	2.4	2.9	0.0	4.3	4.0	3.7	1.6	0.406	0.0	3.0	1.1	4.2	1.1	0.887
Prosaposin	SAP_HUMAN	58 kDa	0.0	0.0	2.4	1.5	0.0	0.0	4.4	3.7	2.1	0.468	0.0	5.3	0.0	1.7	1.8	0.606
Ras-related C3 botulinum toxin substrate 1	RAC1_BOVIN	21 kDa	0.0	2.3	1.8	2.9	0.0	0.0	4.7	6.2	1.5	0.607	0.0	4.6	0.0	2.5	1.0	0.999
Kininogen-2	KNG2_BOVIN	69 kDa	23.6	26.3	17.6	0.0	27.7	20.1	5.1	0.0	0.8	0.693	27.4	12.9	32.8	0.0	1.1	0.885
60S ribosomal protein L10a	RL10A_BOVIN (+1)	25 kDa	0.0	1.1	1.2	2.2	0.6	0.0	2.5	3.7	1.5	0.593	0.0	1.5	1.1	3.3	1.3	0.685
Proteasome subunit beta type-1	PSB1_HUMAN	26 kDa	0.0	2.3	1.8	5.1	0.0	2.9	2.9	2.5	0.9	0.850	2.7	3.0	0.0	5.0	1.2	0.807
Actin, muscle	ACTM_APLCA	42 kDa	0.0	59.3	55.1	59.6	21.6	63.2	50.4	87.5	1.3	0.565	0.0	69.1	40.8	65.6	1.0	0.987
60 kDa heat shock protein, mitochondrial	CH60_HUMAN	61 kDa	0.0	0.0	1.2	4.4	0.0	0.0	1.1	2.5	0.6	0.684	0.0	8.4	0.0	10.8	3.4	0.325
Tropomyosin beta chain	TPM2_HUMAN (+1)	33 kDa	5.4	5.7	5.4	8.1	1.1	5.7	12.3	12.3	1.3	0.583	6.8	12.9	2.3	10.0	1.3	0.490
F-actin-capping protein subunit beta	CAPZB_HUMAN (+4)	31 kDa	0.0	1.1	2.4	5.1	0.0	0.0	4.7	2.5	0.8	0.817	0.0	5.3	0.0	2.5	0.9	0.898
Serum albumin	ALBU_MACFA (+1)	69 kDa	134.2	119.8	67.8	0.0	97.0	127.8	0.0	0.0	0.7	0.608	156.0	49.4	155.1	56.4	1.3	0.596
Tyrosine--tRNA ligase, cytoplasmic	SYYC_HUMAN	59 kDa	0.0	3.4	1.8	4.4	0.0	2.9	1.8	3.7	0.9	0.808	1.4	3.0	0.0	4.2	0.9	0.844
60S ribosomal protein L27	RL27_BOVIN (+1)	16 kDa	0.0	0.0	0.0	5.1	0.0	0.0	3.3	6.2	1.8	0.606	0.0	0.0	0.0	5.8	1.1	0.935
Apolipoprotein E	APOE_BOVIN	36 kDa	3.6	3.4	0.6	2.2	3.3	4.3	0.0	1.2	0.9	0.843	1.4	1.5	1.1	3.3	0.7	0.492
T-complex protein 1 subunit beta	TCPB_HUMAN	57 kDa	0.0	0.0	1.2	5.9	0.0	1.4	2.9	6.2	1.5	0.674	0.0	3.8	1.1	4.2	1.3	0.784
Glucose-6-phosphate 1-dehydrogenase	G6PD_HUMAN	59 kDa	0.0	2.3	1.2	2.9	0.0	0.0	4.7	0.0	0.7	0.763	0.0	3.0	0.0	4.2	1.1	0.885
Spectrin beta chain, non-erythrocytic 1	SPTB2_HUMAN	275 kDa	0.0	0.0	0.0	7.4	0.0	0.0	2.9	1.2	0.6	0.704	0.0	1.5	0.0	4.2	0.8	0.849

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Follistatin-related protein 1	FSTL1_HUMAN (+3)	35 kDa	1.8	1.1	0.6	1.5	0.0	2.9	2.9	1.2	1.4	0.547	0.0	3.0	0.0	0.0	0.6	0.571
72 kDa type IV collagenase	MMP2_HUMAN	74 kDa	1.8	2.3	1.2	1.5	0.0	1.4	0.7	1.2	0.5	0.080	0.0	3.0	2.3	0.8	0.9	0.835
Prothrombin	THRB_BOVIN	71 kDa	0.0	1.1	1.8	0.7	10.0	0.0	0.7	0.0	2.9	0.527	4.1	0.0	2.3	0.0	1.7	0.564
PDZ and LIM domain protein 5	PDLI5_HUMAN	64 kDa	0.0	0.0	1.2	9.6	0.0	0.0	2.9	1.2	0.4	0.533	0.0	0.0	0.0	4.2	0.4	0.547
Proteasome subunit alpha type-1	PSA1_HUMAN (+2)	30 kDa	0.0	2.3	1.8	2.9	0.0	1.4	2.9	2.5	1.0	0.949	0.0	2.3	1.1	3.3	1.0	0.938
Rho GDP-dissociation inhibitor 1	GDIR1_HUMAN	23 kDa	0.0	1.1	3.0	2.2	0.6	1.4	6.2	6.2	2.2	0.291	0.0	3.0	1.1	3.3	1.2	0.795
Four and a half LIM domains protein 2	FHL2_HUMAN	32 kDa	0.0	2.3	1.2	5.9	0.0	1.4	3.6	2.5	0.8	0.768	1.4	2.3	1.1	1.7	0.7	0.607
Far upstream element-binding protein 2	FUBP2_HUMAN	73 kDa	0.0	0.0	0.0	6.6	0.0	0.0	1.1	2.5	0.5	0.686	1.4	3.8	0.0	2.5	1.2	0.894
Fatty acid synthase	FAS_HUMAN	273 kDa	0.0	0.0	1.2	8.1	0.0	0.0	2.9	3.7	0.7	0.770	0.0	3.0	0.0	2.5	0.6	0.677
Zinc finger protein 185	ZN185_HUMAN	74 kDa	0.0	1.1	0.0	3.7	0.0	0.0	3.3	3.7	1.4	0.701	0.0	0.8	1.1	1.7	0.7	0.752
Sulfhydryl oxidase 1	QSOX1_HUMAN	83 kDa	1.8	1.1	1.2	1.5	0.0	2.9	1.5	1.2	1.0	0.975	0.0	3.0	1.1	2.5	1.2	0.737
60S ribosomal protein L18a	RL18A_BOVIN (+1)	21 kDa	0.0	3.4	0.0	6.6	0.0	0.0	2.2	3.7	0.6	0.594	1.4	1.5	1.1	4.2	0.8	0.801
Proteasome subunit beta type-5	PSB5_HUMAN (+1)	28 kDa	0.0	2.3	3.0	3.7	0.0	1.4	4.0	4.9	1.2	0.815	0.0	3.8	0.0	5.0	1.0	0.974
Citrate synthase, mitochondrial	CISY_HUMAN (+1)	52 kDa	0.0	0.0	1.2	0.7	0.0	0.0	1.8	1.2	1.6	0.634	0.0	3.8	0.0	2.5	3.2	0.342
Cysteine-rich protein 2	CRIP2_HUMAN (+1)	22 kDa	0.0	2.3	1.2	3.7	0.0	4.3	4.0	2.5	1.5	0.503	1.4	1.5	1.1	2.5	0.9	0.854
Nuclear migration protein nudC	NUDC_HUMAN	38 kDa	0.0	1.1	1.2	3.7	0.0	1.4	4.0	2.5	1.3	0.698	2.7	1.5	1.1	2.5	1.3	0.619
14-3-3 protein beta/alpha	1433B_HUMAN (+1)	28 kDa	0.0	5.7	14.5	9.6	0.0	7.2	12.3	7.4	0.9	0.862	6.8	9.1	3.4	6.6	0.9	0.787
Proteasome subunit alpha type-4	PSA4_BOVIN (+1)	29 kDa	0.0	0.0	3.0	2.9	0.0	0.0	4.0	4.9	1.5	0.656	0.0	2.3	0.0	1.7	0.7	0.645
Myosin regulatory light chain 12A	ML12A_HUMAN (+6)	20 kDa	0.0	0.0	1.8	6.6	0.0	0.0	5.4	11.1	2.0	0.540	0.0	3.8	0.0	5.0	1.0	0.968
Actin-1	ACT1_ECHGR	42 kDa	63.5	0.0	46.6	48.5	21.1	54.5	38.8	0.0	0.7	0.564	49.3	61.5	36.2	52.3	1.3	0.529

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Spliceosome RNA helicase DDX39B	DX39B_HUMAN (+4)	49 kDa	0.0	0.0	1.2	3.7	0.0	4.3	6.5	1.2	2.5	0.345	0.0	3.8	0.0	1.7	1.1	0.913
X-ray repair cross-complementing protein 6	XRCC6_HUMAN	70 kDa	0.0	0.0	1.8	3.7	0.0	0.0	5.1	0.0	0.9	0.949	0.0	2.3	0.0	1.7	0.7	0.727
Proteasome subunit beta type-6	PSB6_HUMAN	25 kDa	0.0	1.1	1.2	2.9	0.0	4.3	1.5	3.7	1.8	0.415	2.7	3.0	2.3	3.3	2.1	0.082
14-3-3 protein eta	1433F_HUMAN	28 kDa	0.0	5.7	13.9	10.3	0.0	10.0	12.0	8.6	1.0	0.966	5.5	9.9	3.4	6.6	0.8	0.747
Inter-alpha-trypsin inhibitor heavy chain H1	ITIH1_BOVIN	101 kDa	0.0	3.4	1.2	1.5	4.4	2.9	0.0	0.0	1.2	0.828	4.1	0.0	3.4	0.8	1.4	0.665
Far upstream element-binding protein 1	FUBP1_HUMAN	68 kDa	0.0	2.3	0.0	8.1	0.0	1.4	2.2	2.5	0.6	0.621	0.0	2.3	1.1	2.5	0.6	0.609
Ubiquitin-conjugating enzyme E2 variant 1	UB2V1_BOVIN (+1)	16 kDa	0.0	1.1	1.8	2.9	0.0	0.0	2.9	0.0	0.5	0.462	0.0	1.5	0.0	1.7	0.5	0.413
Actin-related protein 2/3 complex subunit 1B	ARC1B_HUMAN	41 kDa	0.0	2.3	1.2	4.4	0.6	1.4	4.4	1.2	1.0	0.950	1.4	1.5	1.1	1.7	0.7	0.596
Retinol-binding protein 4	RET4_BOVIN	21 kDa	5.4	2.3	1.2	0.0	5.0	4.3	0.0	0.0	1.0	0.961	6.8	0.0	4.5	0.0	1.3	0.779
Cytoplasmic dynein 1 intermediate chain 2	DC1I2_HUMAN	71 kDa	0.0	0.0	1.2	5.9	0.0	0.0	2.2	2.5	0.7	0.712	0.0	4.6	1.1	4.2	1.4	0.716
Annexin A5	ANXA5_HUMAN	36 kDa	0.0	0.0	3.0	1.5	0.6	0.0	2.5	0.0	0.7	0.723	0.0	2.3	0.0	3.3	1.2	0.812
Poly(rC)-binding protein 1	PCBP1_BOVIN	37 kDa	0.0	2.3	1.8	2.9	0.0	1.4	2.2	2.5	0.9	0.783	0.0	1.5	0.0	2.5	0.6	0.422
Fibrinogen alpha chain	FIBA_BOVIN	67 kDa	0.0	1.1	0.6	0.0	6.7	1.4	0.7	0.0	5.0	0.329	0.0	0.0	3.4	0.0	1.9	0.670
Chaperone protein DnaK	DNAK_MYCPU	66 kDa	0.0	0.0	3.6	2.2	0.6	0.0	4.4	3.7	1.5	0.643	0.0	1.5	1.1	2.5	0.9	0.873
Neuronal cell adhesion molecule	NRCAM_HUMAN	144 kDa	7.3	1.1	0.0	5.1	0.0	0.0	0.7	0.0	0.1	0.155	2.7	0.0	0.0	0.8	0.3	0.244
EF-hand domain-containing protein D2	EFHD2_HUMAN	27 kDa	0.0	3.4	0.0	5.9	0.0	0.0	1.8	3.7	0.6	0.597	0.0	3.8	0.0	4.2	0.9	0.860
Aspartate aminotransferase, mitochondrial	AATM_MACFA (+1)	47 kDa	1.8	0.0	2.4	0.0	0.0	0.0	3.6	2.5	1.4	0.691	0.0	6.1	0.0	5.0	2.6	0.381
DNA-(apurinic or apyrimidinic site) lyase	APEX1_PANPA	36 kDa	0.0	1.1	3.6	4.4	0.0	0.0	1.5	1.2	0.3	0.219	0.0	3.0	0.0	2.5	0.6	0.513
40S ribosomal protein S10	RS10_BOVIN (+1)	19 kDa	0.0	0.0	1.8	3.7	0.0	0.0	4.7	2.5	1.3	0.779	0.0	0.8	0.0	1.7	0.4	0.468

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
S-formylglutathione hydrolase	ESTD_HUMAN	31 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.9	0.0	2.0	0.680	0.0	0.0	0.0	0.0	0.0	0.391
Tetranectin	TETN_BOVIN	22 kDa	0.0	3.4	1.8	0.0	3.9	4.3	0.4	1.2	1.9	0.408	4.1	1.5	2.3	0.0	1.5	0.597
Peroxiredoxin-2	PRDX2_HUMAN (+1)	22 kDa	0.0	6.8	4.2	6.6	0.0	2.9	7.3	8.6	1.1	0.922	0.0	5.3	0.0	5.0	0.6	0.428
Stress-70 protein, mitochondrial	GRP75_HUMAN (+2)	74 kDa	0.0	0.0	1.8	0.0	0.0	0.0	2.2	0.0	1.2	0.903	0.0	6.1	0.0	4.2	5.6	0.266
Glycine--tRNA ligase	SYG_HUMAN	83 kDa	0.0	0.0	1.2	5.1	0.0	0.0	5.4	2.5	1.2	0.835	0.0	1.5	0.0	0.8	0.4	0.481
Insulin-like growth factor-binding protein 2	IBP2_HUMAN	35 kDa	0.0	0.0	1.2	2.9	0.6	0.0	0.7	1.2	0.6	0.611	0.0	2.3	0.0	0.0	0.5	0.622
Protein CDV3 homolog	CDV3_HUMAN	27 kDa	0.0	2.3	1.2	2.9	0.0	1.4	3.3	1.2	0.9	0.897	0.0	4.6	0.0	0.8	0.8	0.844
Ribonuclease inhibitor	RINI_HUMAN	50 kDa	0.0	1.1	0.6	5.1	0.0	0.0	3.6	2.5	0.9	0.897	0.0	1.5	0.0	2.5	0.6	0.609
Band 4.1-like protein 3	E41L3_HUMAN	121 kDa	0.0	1.1	1.2	4.4	0.0	1.4	2.5	3.7	1.1	0.860	0.0	3.8	1.1	4.2	1.3	0.691
Septin-9	SEPT9_HUMAN	65 kDa	0.0	3.4	0.6	3.7	0.0	2.9	1.8	2.5	0.9	0.907	0.0	3.8	0.0	4.2	1.0	0.969
LIM and SH3 domain protein 1	LASP1_PONAB	30 kDa	0.0	1.1	0.6	3.7	0.0	0.0	3.3	1.2	0.8	0.843	0.0	1.5	0.0	1.7	0.6	0.574
Superoxide dismutase [Cu-Zn]	SODC_HUMAN	16 kDa	0.0	0.0	4.2	1.5	0.0	0.0	2.9	1.2	0.7	0.758	0.0	1.5	0.0	0.0	0.3	0.385
40S ribosomal protein S15a	RS15A_BOVIN (+1)	15 kDa	0.0	0.0	0.6	3.7	0.0	0.0	2.9	2.5	1.3	0.826	0.0	0.8	0.0	5.8	1.5	0.743
Proteasome subunit beta type-7	PSB7_HUMAN	30 kDa	0.0	1.1	1.8	3.7	0.0	1.4	1.1	2.5	0.8	0.673	0.0	3.8	0.0	3.3	1.1	0.928
60S ribosomal protein L14	RL14_HUMAN	23 kDa	0.0	0.0	0.0	5.9	0.0	0.0	1.5	4.9	1.1	0.950	0.0	1.5	0.0	3.3	0.8	0.882
Proteasome subunit alpha type-6	PSA6_BOVIN	27 kDa	0.0	0.0	0.0	2.9	0.0	0.0	4.4	2.5	2.3	0.483	0.0	1.5	0.0	0.8	0.8	0.865
60S ribosomal protein L17	RL17_BOVIN (+2)	21 kDa	0.0	0.0	0.0	6.6	0.0	0.0	0.0	2.5	0.4	0.589	0.0	0.0	0.0	7.5	1.1	0.935
Eukaryotic translation initiation factor 2 subunit 3	IF2G_HUMAN (+1)	51 kDa	0.0	0.0	0.0	8.1	0.0	0.0	1.5	2.5	0.5	0.650	0.0	2.3	0.0	2.5	0.6	0.719
Lupus La protein	LA_HUMAN	47 kDa	0.0	1.1	0.6	3.7	0.0	1.4	1.5	2.5	1.0	0.985	1.4	3.0	0.0	3.3	1.4	0.625
40S ribosomal protein S15	RS15_CHICK (+1)	17 kDa	0.0	0.0	1.2	4.4	0.0	0.0	1.1	6.2	1.3	0.830	0.0	2.3	1.1	5.0	1.5	0.659

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Exportin-2	XPO2_HUMAN (+3)	110 kDa	0.0	2.3	0.0	4.4	0.0	0.0	0.4	0.0	0.1	0.232	0.0	3.0	0.0	2.5	0.8	0.834
Nucleolin	NUCL_HUMAN (+2)	77 kDa	0.0	0.0	0.0	8.8	0.0	0.0	2.2	0.0	0.2	0.512	0.0	0.0	0.0	6.6	0.8	0.850
Transthyretin	TTHY_BOVIN	16 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Hsp90 co-chaperone Cdc37	CDC37_HUMAN	44 kDa	0.0	2.3	2.4	1.5	0.0	1.4	1.5	2.5	0.9	0.793	2.7	1.5	2.3	1.7	1.3	0.462
RNA-binding protein EWS	EWS_MOUSE	68 kDa	0.0	2.3	1.2	2.9	0.0	1.4	1.1	2.5	0.8	0.675	0.0	2.3	1.1	1.7	0.8	0.688
Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	PLOD2_HUMAN	85 kDa	1.8	1.1	0.6	2.9	0.0	0.0	0.7	2.5	0.5	0.324	1.4	3.0	1.1	3.3	1.4	0.465
Isocitrate dehydrogenase [NADP] cytoplasmic	IDHC_HUMAN (+1)	47 kDa	0.0	1.1	0.6	3.7	0.0	1.4	2.5	1.2	1.0	0.957	0.0	1.5	0.0	2.5	0.7	0.740
Histone H2B type 1-C/E/F/G/I	H2B1C_HUMAN (+16)	14 kDa	0.0	0.0	1.2	0.7	0.6	0.0	1.8	0.0	1.2	0.847	0.0	3.0	0.0	1.7	2.4	0.435
Elongation factor 1-beta	EF1B_HUMAN (+1)	25 kDa	0.0	1.1	0.6	2.9	0.0	0.0	3.3	1.2	1.0	0.963	0.0	3.8	0.0	3.3	1.5	0.637
Keratin, type II cytoskeletal 6A	K2C6A_HUMAN	60 kDa	0.0	0.0	0.0	0.0	0.6	0.0	12.3	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Dihydropyrimidinase-related protein 2	DPYL2_HUMAN	62 kDa	0.0	0.0	1.2	0.0	0.0	0.0	8.0	0.0	6.6	0.461	0.0	0.0	0.0	0.0	0.0	0.391
Apolipoprotein M	APOM_HUMAN	21 kDa	1.8	1.1	0.6	0.7	0.0	1.4	0.0	0.0	0.3	0.167	0.0	0.8	0.0	0.8	0.4	0.107
Keratin, type II cytoskeletal 2 epidermal	K22E_HUMAN	65 kDa	1.8	0.0	0.0	0.0	1.1	8.6	8.0	4.9	12.5	0.052	0.0	0.0	0.0	2.5	1.4	0.834
Proteasome subunit alpha type-3	PSA3_HUMAN (+3)	28 kDa	0.0	2.3	1.2	2.2	0.0	2.9	2.2	2.5	1.3	0.608	2.7	3.0	0.0	2.5	1.5	0.495
Heat shock 70 kDa protein 1A/1B	HSP71_HUMAN (+4)	70 kDa	0.0	8.0	1.8	4.4	1.1	5.7	5.4	6.2	1.3	0.634	6.8	3.8	3.4	6.6	1.5	0.451
Dihydropyrimidinase-related protein 3	DPYL3_HUMAN	62 kDa	0.0	1.1	1.2	1.5	0.0	0.0	4.4	1.2	1.5	0.706	0.0	1.5	0.0	0.8	0.6	0.482
6-phosphofructokinase type C	K6PP_HUMAN	86 kDa	0.0	0.0	1.2	1.5	0.0	0.0	4.7	1.2	2.2	0.530	0.0	1.5	0.0	0.8	0.9	0.882
Apolipoprotein D	APOD_BOVIN	21 kDa	0.0	1.1	0.0	0.7	3.3	1.4	0.4	0.0	2.7	0.369	0.0	0.8	1.1	0.8	1.5	0.591
Calumenin	CALU_HUMAN (+1)	37 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.8	2.5	2.9	0.383	0.0	4.6	0.0	2.5	4.8	0.302

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
T-complex protein 1 subunit zeta	TCPZ_HUMAN (+1)	58 kDa	0.0	0.0	0.0	4.4	0.0	0.0	2.9	1.2	0.9	0.959	0.0	0.8	0.0	1.7	0.5	0.694
Microtubule-associated protein 1B	MAP1B_HUMAN	271 kDa	0.0	0.0	0.0	11.8	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	1.7	0.1	0.455
Tyrosine-protein kinase receptor UFO	UFO_HUMAN	98 kDa	3.6	0.0	1.2	1.5	0.6	0.0	1.1	2.5	0.7	0.574	1.4	0.0	1.1	0.8	0.5	0.412
Cathelicidin-4	CTHL4_BOVIN	16 kDa	1.8	1.1	0.0	1.5	0.0	1.4	0.7	0.0	0.5	0.321	0.0	1.5	0.0	0.8	0.5	0.372
1,4-alpha-glucan-branching enzyme	GLGB_HUMAN	80 kDa	0.0	2.3	0.6	2.9	0.0	1.4	1.8	2.5	1.0	0.974	0.0	1.5	0.0	1.7	0.5	0.460
Eukaryotic translation initiation factor 2A	EIF2A_HUMAN	65 kDa	0.0	1.1	0.0	4.4	0.0	1.4	1.1	2.5	0.9	0.908	0.0	3.0	0.0	2.5	1.0	0.996
Glucosidase 2 subunit beta	GLU2B_HUMAN	59 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.8	2.5	2.9	0.383	1.4	3.8	1.1	1.7	5.4	0.073
SAP domain-containing ribonucleoprotein	SARNP_HUMAN	24 kDa	0.0	0.0	0.0	2.9	0.0	0.0	2.2	0.0	0.7	0.842	0.0	1.5	0.0	0.8	0.8	0.865
60S acidic ribosomal protein P2	RLA2_HUMAN (+1)	12 kDa	0.0	0.0	0.0	8.1	0.0	0.0	0.4	1.2	0.2	0.483	0.0	0.0	0.0	5.8	0.7	0.827
60S ribosomal protein L34	RL34_HUMAN (+5)	13 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.7	4.9	1.5	0.754	0.0	0.0	0.0	5.0	1.4	0.841
40S ribosomal protein S11	RS11_BOVIN (+1)	18 kDa	0.0	0.0	0.0	3.7	0.0	0.0	2.5	3.7	1.7	0.642	0.0	0.0	0.0	3.3	0.9	0.945
Actin-related protein 2/3 complex subunit 2	ARPC2_HUMAN (+3)	34 kDa	0.0	0.0	0.6	0.0	0.0	0.0	5.1	0.0	8.4	0.445	0.0	2.3	0.0	0.0	3.8	0.523
Heterogeneous nuclear ribonucleoprotein A3	ROA3_HUMAN (+1)	40 kDa	0.0	1.1	1.8	5.9	0.0	1.4	7.6	1.2	1.2	0.872	0.0	3.8	0.0	0.8	0.5	0.529
Drebrin-like protein	DBNL_HUMAN	48 kDa	0.0	0.0	0.6	4.4	0.0	1.4	2.9	1.2	1.1	0.914	0.0	2.3	1.1	2.5	1.2	0.863
Y-box-binding protein 3	YBOX3_HUMAN	40 kDa	0.0	0.0	0.6	5.1	0.0	1.4	1.5	4.9	1.4	0.762	0.0	3.8	0.0	4.2	1.4	0.757
Heterogeneous nuclear ribonucleoprotein Q	HNRPQ_MOUSE	70 kDa	0.0	0.0	0.6	2.9	0.0	0.0	2.9	2.5	1.5	0.679	0.0	3.0	0.0	1.7	1.3	0.786
Actin-related protein 2-A	ARP2A_DANRE (+7)	45 kDa	0.0	0.0	0.6	2.2	0.0	0.0	7.3	0.0	2.6	0.592	0.0	0.8	0.0	0.0	0.3	0.410
Keratin, type I cytoskeletal 13	K1C13_HUMAN	50 kDa	0.0	0.0	0.0	0.0	0.0	0.0	11.2	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Tyrosine-protein kinase receptor Tie-1	**TIE1_HUMAN**	**125 kDa**	**1.8**	**2.3**	**0.6**	**1.5**	**0.0**	**0.0**	**0.4**	**0.0**	**0.1**	**0.023**	1.4	1.5	1.1	0.0	0.7	0.318
Tissue-type plasminogen activator	TPA_HUMAN	63 kDa	1.8	0.0	0.6	2.9	0.6	2.9	1.8	1.2	1.2	0.746	1.4	3.0	3.4	0.8	1.6	0.401

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
40S ribosomal protein S28	RS28_BOVIN	8 kDa	0.0	1.1	0.0	2.2	0.0	0.0	2.2	2.5	1.4	0.719	0.0	1.5	0.0	4.2	1.7	0.626
BAG family molecular chaperone regulator 3	BAG3_HUMAN	62 kDa	0.0	1.1	0.6	2.2	0.0	1.4	0.7	0.0	0.5	0.472	1.4	2.3	0.0	0.8	1.1	0.851
Proteasome subunit beta type-2	PSB2_HUMAN	23 kDa	0.0	1.1	1.2	3.7	0.0	1.4	1.1	2.5	0.8	0.790	0.0	3.0	0.0	1.7	0.8	0.766
40S ribosomal protein S5a	RS5A_DROME (+1)	25 kDa	0.0	0.0	2.4	2.2	0.6	0.0	1.8	2.5	1.0	0.955	0.0	0.8	0.0	1.7	0.5	0.510
Threonine--tRNA ligase, cytoplasmic	SYTC_HUMAN	83 kDa	0.0	1.1	1.2	0.7	0.0	2.9	4.0	0.0	2.2	0.429	1.4	1.5	1.1	0.0	1.3	0.618
Cell surface glycoprotein MUC18	MUC18_HUMAN	72 kDa	0.0	0.0	2.4	1.5	1.1	0.0	4.0	1.2	1.6	0.580	0.0	2.3	0.0	0.0	0.6	0.642
Histidine--tRNA ligase, cytoplasmic	SYHC_HUMAN (+1)	57 kDa	0.0	1.1	0.0	2.9	0.0	1.4	3.6	1.2	1.5	0.609	0.0	2.3	0.0	2.5	1.2	0.867
Calpastatin	ICAL_HUMAN	77 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.7	1.2	0.7	0.772	0.0	0.8	0.0	1.7	0.8	0.882
Neutral alpha-glucosidase AB	GANAB_HUMAN (+1)	107 kDa	0.0	0.0	0.0	0.7	0.0	1.4	2.2	0.0	4.9	0.283	1.4	1.5	0.0	0.8	5.1	0.119
Proteasome subunit alpha type-7	PSA7_HUMAN	28 kDa	0.0	0.0	1.8	4.4	0.0	0.0	3.3	0.0	0.5	0.597	0.0	0.8	0.0	0.0	0.1	0.283
Fructose-bisphosphate aldolase C	ALDOC_HUMAN (+2)	39 kDa	0.0	0.0	2.4	0.7	0.0	0.0	4.4	0.0	1.4	0.818	0.0	2.3	0.0	1.7	1.2	0.819
Tryptophan--tRNA ligase, cytoplasmic	SYWC_HUMAN (+1)	53 kDa	0.0	0.0	0.6	0.0	0.0	0.0	4.7	0.0	7.8	0.449	0.0	0.0	0.0	0.0	0.0	0.391
40S ribosomal protein S19	RS19_BOVIN (+2)	16 kDa	0.0	0.0	1.2	0.7	0.0	0.0	4.4	2.5	3.5	0.338	0.0	0.8	0.0	0.8	0.8	0.821
Phosphoserine aminotransferase	SERC_HUMAN	40 kDa	0.0	1.1	0.6	3.7	0.0	0.0	2.9	0.0	0.5	0.583	0.0	0.8	0.0	1.7	0.4	0.447
Inosine-5'-monophosphate dehydrogenase 2	IMDH2_HUMAN	56 kDa	0.0	0.0	2.4	4.4	0.0	0.0	3.6	0.0	0.5	0.588	0.0	1.5	0.0	1.7	0.5	0.475
Heterogeneous nuclear ribonucleoprotein A/B	ROAA_MOUSE	31 kDa	0.0	0.0	3.0	5.9	0.0	0.0	4.4	3.7	0.9	0.911	1.4	5.3	0.0	5.8	1.4	0.672
Protein S100-A13	S10AD_HUMAN	11 kDa	0.0	1.1	0.6	2.2	0.0	1.4	1.5	1.2	1.0	0.946	0.0	1.5	0.0	2.5	1.0	0.986
Coronin-1C	COR1C_HUMAN	53 kDa	0.0	1.1	0.6	2.2	0.0	1.4	2.9	1.2	1.4	0.614	0.0	1.5	1.1	1.7	1.1	0.886
UV excision repair protein RAD23 homolog B	RD23B_HUMAN	43 kDa	0.0	2.3	0.0	5.1	0.0	0.0	2.5	0.0	0.3	0.419	1.4	1.5	0.0	0.0	0.4	0.433

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Importin-5	IPO5_HUMAN	124 kDa	0.0	1.1	0.0	4.4	0.0	0.0	1.5	1.2	0.5	0.556	0.0	1.5	0.0	1.7	0.6	0.629
Eukaryotic initiation factor 4A-II	IF4A2_BOVIN (+1)	46 kDa	0.0	0.0	7.3	8.1	0.0	0.0	11.6	8.6	1.3	0.755	0.0	9.1	0.0	8.3	1.1	0.883
Thioredoxin reductase 1, cytoplasmic	TRXR1_HUMAN (+1)	71 kDa	0.0	0.0	1.8	0.0	0.6	0.0	4.0	0.0	2.5	0.554	0.0	0.0	0.0	0.0	0.0	0.391
60S acidic ribosomal protein P0	RLA0_HUMAN (+4)	34 kDa	0.0	0.0	0.0	6.6	0.0	0.0	1.8	2.5	0.6	0.758	0.0	0.0	0.0	4.2	0.6	0.765
Rho-related GTP-binding protein RhoC	RHOC_BOVIN	22 kDa	0.0	1.1	1.2	2.2	0.0	1.4	2.2	1.2	1.1	0.914	0.0	1.5	0.0	1.7	0.7	0.612
BTB/POZ domain-containing protein KCTD12	KCD12_HUMAN	36 kDa	0.0	0.0	1.8	3.7	0.0	1.4	2.5	0.0	0.7	0.737	0.0	1.5	1.1	1.7	0.8	0.773
Src substrate cortactin	SRC8_HUMAN	62 kDa	0.0	1.1	0.6	2.9	0.0	0.0	2.9	2.5	1.1	0.872	0.0	1.5	0.0	0.8	0.5	0.462
Chloride intracellular channel protein 4	CLIC4_HUMAN (+4)	29 kDa	0.0	1.1	1.8	2.9	0.0	0.0	2.9	0.0	0.5	0.462	0.0	1.5	0.0	0.8	0.4	0.272
Complement factor H	CFAH_BOVIN	140 kDa	0.0	1.1	1.2	0.7	3.3	0.0	0.0	0.0	1.1	0.949	1.4	0.0	0.0	0.0	0.4	0.369
Hepatoma-derived growth factor	HDGF_HUMAN	27 kDa	0.0	0.0	0.0	4.4	0.0	0.0	1.5	3.7	1.2	0.901	0.0	3.0	0.0	1.7	1.1	0.959
40S ribosomal protein S23	RS23_BOVIN (+5)	16 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.2	3.7	4.0	0.322	0.0	0.0	0.0	2.5	1.7	0.739
Asparagine--tRNA ligase, cytoplasmic	SYNC_HUMAN	63 kDa	0.0	0.0	0.6	2.2	0.0	0.0	4.7	0.0	1.7	0.730	0.0	0.8	0.0	0.8	0.6	0.619
Fumarate hydratase, mitochondrial	FUMH_HUMAN (+1)	55 kDa	0.0	0.0	0.6	1.5	0.0	1.4	1.5	1.2	2.0	0.339	1.4	1.5	1.1	2.5	3.1	0.053
40S ribosomal protein S7	RS7_BOVIN	22 kDa	0.0	0.0	1.2	1.5	0.6	0.0	1.8	1.2	1.3	0.694	0.0	1.5	0.0	3.3	1.8	0.571
Elongation factor 1-delta	EF1D_HUMAN	31 kDa	0.0	0.0	0.0	5.1	0.0	0.0	2.2	2.5	0.9	0.934	0.0	1.5	0.0	2.5	0.8	0.851
Serum albumin	ALBU_SHEEP	69 kDa	596.7	332.1	0.0	111.8	502.4	0.0	125.2	0.0	0.6	0.582	0.0	235.4	0.0	217.5	0.4	0.370
ADP-ribosylation factor 4	ARF4_HUMAN	21 kDa	0.0	2.3	0.6	2.2	0.0	1.4	1.5	2.5	1.1	0.936	0.0	1.5	0.0	2.5	0.8	0.758
Microtubule-associated protein RP/EB family member 1	MARE1_HUMAN	30 kDa	0.0	1.1	0.0	0.0	0.0	0.0	3.3	0.0	2.9	0.575	0.0	0.0	0.0	0.0	0.0	0.391
Stathmin	STMN1_BOVIN (+1)	17 kDa	0.0	0.0	1.2	1.5	0.0	0.0	4.4	3.7	3.0	0.343	0.0	1.5	0.0	0.8	0.9	0.882

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Hsc70-interacting protein	F10A1_HUMAN (+1)	41 kDa	0.0	0.0	0.0	5.1	0.0	0.0	2.2	0.0	0.4	0.623	0.0	0.0	0.0	1.7	0.3	0.558
Puromycin-sensitive aminopeptidase	PSA_HUMAN	103 kDa	0.0	0.0	0.6	1.5	0.0	0.0	2.9	0.0	1.4	0.809	0.0	0.8	0.0	0.0	0.4	0.447
NSFL1 cofactor p47	NSF1C_HUMAN	41 kDa	0.0	0.0	0.6	2.9	0.0	1.4	1.1	1.2	1.1	0.949	0.0	2.3	0.0	2.5	1.3	0.766
60S ribosomal protein L11	RL11_BOVIN (+1)	20 kDa	0.0	0.0	1.8	0.7	0.0	0.0	2.2	3.7	2.3	0.450	0.0	0.8	0.0	2.5	1.3	0.819
DNA-dependent protein kinase catalytic subunit	PRKDC_HUMAN	469 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	2.5	1.1	0.940	0.0	2.3	0.0	3.3	2.5	0.434
Serpin B9	SPB9_HUMAN	42 kDa	0.0	0.0	0.6	0.7	0.0	0.0	3.6	1.2	3.6	0.383	0.0	0.8	0.0	0.0	0.6	0.613
Septin-7	SEPT7_BOVIN (+4)	51 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.5	0.0	1.2	0.924	0.0	0.0	0.0	0.8	0.4	0.592
60S ribosomal protein L38	RL38_BOVIN (+2)	8 kDa	0.0	0.0	1.8	0.0	0.0	0.0	2.5	0.0	1.4	0.825	0.0	0.0	0.0	0.0	0.0	0.391
Ezrin	EZRI_HUMAN	69 kDa	0.0	0.0	12.1	8.8	0.0	0.0	19.2	20.9	1.9	0.501	0.0	15.9	0.0	0.0	0.8	0.814
SH3 domain-binding glutamic acid-rich-like protein	SH3L1_HUMAN (+1)	13 kDa	0.0	2.3	0.6	1.5	0.0	1.4	1.5	2.5	1.2	0.739	0.0	0.8	0.0	1.7	0.6	0.477
Serine--tRNA ligase, cytoplasmic	SYSC_HUMAN (+1)	59 kDa	0.0	1.1	0.0	2.2	0.0	1.4	2.2	1.2	1.4	0.611	0.0	0.8	0.0	0.0	0.2	0.318
26S proteasome non-ATPase regulatory subunit 11	PSD11_BOVIN (+1)	47 kDa	0.0	2.3	0.0	1.5	0.0	0.0	1.5	1.2	0.7	0.712	0.0	3.0	0.0	1.7	1.3	0.808
Ras-related protein Rab-11A	RB11A_BOVIN (+5)	24 kDa	0.0	0.0	0.6	2.9	0.0	0.0	1.8	1.2	0.9	0.886	0.0	0.8	0.0	2.5	0.9	0.938
Cadherin-5	CADH5_HUMAN	88 kDa	0.0	1.1	3.0	0.0	0.0	0.0	2.9	1.2	1.0	0.993	0.0	0.8	0.0	0.0	0.2	0.323
40S ribosomal protein S6	RS6_HUMAN (+2)	29 kDa	0.0	0.0	0.6	3.7	0.0	0.0	0.7	2.5	0.7	0.806	0.0	0.0	0.0	4.2	1.0	0.982
Histone H1.2	H12_HUMAN (+8)	21 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.5	2.5	1.3	0.807	0.0	1.5	0.0	1.7	1.1	0.948
60S ribosomal protein L35a	RL35A_HUMAN (+2)	13 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.4	3.7	1.1	0.943	0.0	0.0	0.0	3.3	0.9	0.945
Fermitin family homolog 3	URP2_HUMAN	76 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.5	0.0	1.2	0.924	0.0	0.0	0.0	0.0	0.0	0.391
60S ribosomal protein L7a	RL7A_HUMAN (+1)	30 kDa	0.0	0.0	0.0	5.9	0.0	0.0	1.1	3.7	0.8	0.879	0.0	0.0	0.0	2.5	0.4	0.623

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Protein AHNAK2	AHNK2_HUMAN	617 kDa	0.0	0.0	0.0	3.7	0.0	0.0	2.5	1.2	1.0	0.984	0.0	1.5	0.0	0.0	0.4	0.616
60S ribosomal protein L4	RL4_HUMAN (+1)	48 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.8	0.0	1.2	0.888	0.0	0.0	0.0	2.5	1.7	0.739
Cellular nucleic acid-binding protein	CNBP_HUMAN (+1)	19 kDa	0.0	1.1	0.6	2.2	0.0	1.4	1.8	1.2	1.1	0.836	0.0	1.5	0.0	0.8	0.6	0.527
Peptidyl-prolyl cis-trans isomerase FKBP4	FKBP4_HUMAN	52 kDa	0.0	0.0	0.6	4.4	0.0	1.4	1.1	0.0	0.5	0.611	1.4	0.8	0.0	1.7	0.8	0.799
60S ribosomal protein L15	RL15_BOVIN	24 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.5	0.0	0.5	0.671	0.0	0.0	0.0	2.5	0.8	0.911
Calpain small subunit 1	CPNS1_HUMAN (+3)	28 kDa	0.0	2.3	0.6	2.9	0.0	1.4	0.7	2.5	0.8	0.741	0.0	1.5	0.0	1.7	0.5	0.460
High mobility group protein HMGI-C	HMGA2_HUMAN	12 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.7	3.7	2.0	0.617	0.0	2.3	1.1	1.7	2.3	0.367
Hypoxia up-regulated protein 1	HYOU1_HUMAN	111 kDa	0.0	0.0	1.2	0.7	0.0	0.0	0.4	2.5	1.5	0.755	0.0	2.3	1.1	2.5	3.0	0.194
Phenylalanine--tRNA ligase alpha subunit	SYFA_HUMAN (+1)	58 kDa	0.0	1.1	0.6	2.9	0.0	0.0	0.7	2.5	0.7	0.679	0.0	3.0	0.0	2.5	1.2	0.845
60S ribosomal protein L23a	RL23A_BOVIN	18 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.5	2.5	1.1	0.959	0.0	0.8	0.0	1.7	0.7	0.769
Heterogeneous nuclear ribonucleoprotein L	HNRPL_HUMAN	64 kDa	0.0	1.1	0.0	3.7	0.0	0.0	1.1	0.0	0.2	0.369	0.0	0.8	0.0	0.8	0.3	0.427
Eukaryotic translation initiation factor 4H	IF4H_HUMAN (+3)	27 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.1	2.5	1.0	0.978	0.0	1.5	0.0	2.5	1.1	0.943
Alanine--tRNA ligase, cytoplasmic	SYAC_HUMAN	107 kDa	0.0	1.1	0.0	4.4	0.0	0.0	1.5	1.2	0.5	0.556	0.0	0.8	0.0	1.7	0.4	0.523
Proteasome subunit alpha type-5	PSA5_BOVIN (+1)	26 kDa	0.0	0.0	0.6	1.5	0.0	0.0	3.6	1.2	2.3	0.493	0.0	0.0	0.0	0.8	0.4	0.477
Coatomer subunit beta'	COPB2_HUMAN	102 kDa	0.0	0.0	0.0	5.9	0.0	0.0	0.4	0.0	0.1	0.418	0.0	0.8	0.0	1.7	0.4	0.605
Thyroxine-binding globulin	THBG_BOVIN	46 kDa	0.0	0.0	0.0	0.0	4.4	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Valine--tRNA ligase	SYVC_HUMAN	140 kDa	0.0	1.1	0.6	2.2	0.0	1.4	0.4	0.0	0.5	0.391	0.0	0.8	1.1	0.8	0.7	0.587
UDP-N-acetylhexosamine pyrophosphorylase	UAP1_HUMAN	59 kDa	0.0	1.1	0.0	1.5	0.0	0.0	1.5	1.2	1.0	0.975	0.0	1.5	0.0	2.5	1.5	0.649
60S ribosomal protein L22	RL22_HUMAN (+2)	15 kDa	0.0	0.0	0.0	4.4	0.0	0.0	1.5	0.0	0.3	0.562	0.0	0.8	0.0	2.5	0.7	0.826

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Probable ATP-dependent RNA helicase DDX17	DDX17_HUMAN (+1)	80 kDa	0.0	0.0	0.6	1.5	0.0	0.0	2.2	3.7	2.8	0.384	0.0	1.5	0.0	2.5	1.9	0.524
Importin subunit beta-1	IMB1_HUMAN	97 kDa	0.0	1.1	0.6	3.7	0.0	0.0	0.7	0.0	0.1	0.243	0.0	0.8	0.0	1.7	0.4	0.447
Ubiquitin carboxyl-terminal hydrolase 14	UBP14_HUMAN (+1)	56 kDa	0.0	0.0	0.6	1.5	0.0	0.0	1.5	0.0	0.7	0.766	0.0	0.8	0.0	0.8	0.8	0.782
Poly(rC)-binding protein 2	PCBP2_HUMAN (+1)	39 kDa	0.0	2.3	2.4	4.4	0.0	0.0	2.2	2.5	0.5	0.361	0.0	2.3	0.0	2.5	0.5	0.378
40S ribosomal protein S17-like	RS17L_HUMAN (+4)	16 kDa	0.0	0.0	0.6	2.2	0.0	0.0	1.5	2.5	1.4	0.741	0.0	0.0	0.0	1.7	0.6	0.682
Phosphatidylethanolamine-binding protein 1	PEBP1_HUMAN	21 kDa	0.0	0.0	2.4	0.7	0.0	0.0	3.6	0.0	1.1	0.917	0.0	0.8	0.0	0.0	0.2	0.381
Polymerase I and transcript release factor	PTRF_HUMAN	43 kDa	0.0	0.0	0.0	6.6	0.0	0.0	1.1	0.0	0.2	0.467	0.0	0.0	0.0	1.7	0.3	0.515
Tubulin-specific chaperone A	TBCA_HUMAN	13 kDa	0.0	0.0	1.2	3.7	0.0	0.0	2.9	0.0	0.6	0.676	0.0	0.0	0.0	0.0	0.0	0.253
Caprin-1	CAPR1_HUMAN	78 kDa	0.0	1.1	0.0	2.2	0.0	1.4	0.7	2.5	1.4	0.683	0.0	1.5	1.1	0.8	1.0	0.959
Epididymal secretory protein E1	NPC2_HUMAN	17 kDa	1.8	0.0	0.6	2.2	0.0	0.0	0.0	1.2	0.3	0.217	1.4	2.3	0.0	1.7	1.1	0.817
60S ribosomal protein L9	RL9_HUMAN (+3)	22 kDa	0.0	1.1	0.0	0.7	0.0	0.0	1.8	1.2	1.6	0.609	0.0	0.8	0.0	0.8	0.8	0.851
Serpin H1	SERPH_HUMAN (+1)	46 kDa	0.0	0.0	0.0	0.7	1.1	0.0	1.8	1.2	5.7	0.107	0.0	3.0	0.0	1.7	6.4	0.273
Paxillin	PAXI_HUMAN	65 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.1	0.0	0.4	0.588	0.0	0.8	0.0	1.7	0.8	0.882
Transcription intermediary factor 1-beta	TIF1B_HUMAN	89 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.9	0.0	1.3	0.855	0.0	0.8	0.0	0.8	0.7	0.809
Mitotic checkpoint protein BUB3	BUB3_HUMAN (+2)	37 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.5	1.2	0.9	0.941	0.0	1.5	0.0	0.8	0.8	0.865
Ras-related protein Rab-7a	RAB7A_HUMAN (+4)	23 kDa	0.0	0.0	0.6	0.7	0.0	0.0	2.5	0.0	1.9	0.678	0.0	2.3	0.0	0.0	1.7	0.718
Translationally-controlled tumor protein	TCTP_HUMAN (+2)	20 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.9	0.0	2.0	0.680	0.0	0.0	0.0	0.8	0.6	0.721
Complement component C7	CO7_BOVIN	93 kDa	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0	N/A	N/A	0.0	0.0	1.1	0.0	N/A	N/A
Hemoglobin subunit beta	HBB_BOVIN	16 kDa	0.0	18.3	11.5	0.0	16.6	0.0	5.4	0.0	0.7	0.759	19.2	0.0	18.1	0.0	1.3	0.798

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Proliferating cell nuclear antigen	PCNA_HUMAN (+2)	29 kDa	0.0	0.0	1.8	0.7	0.0	0.0	1.8	1.2	1.2	0.850	0.0	0.8	0.0	0.8	0.6	0.644
60S ribosomal protein L31	RL31_BOVIN	14 kDa	0.0	0.0	0.6	1.5	0.0	0.0	1.5	0.0	0.7	0.766	0.0	0.0	0.0	1.7	0.8	0.854
Protein transport protein Sec23A	SC23A_BOVIN	87 kDa	0.0	0.0	0.0	1.5	0.0	0.0	3.3	0.0	2.2	0.642	0.0	0.8	0.0	0.8	1.1	0.948
S-adenosylmethionine synthase isoform type-2	METK2_HUMAN (+2)	44 kDa	0.0	0.0	0.0	3.7	0.0	0.0	2.2	0.0	0.6	0.740	0.0	0.0	0.0	1.7	0.5	0.642
X-ray repair cross-complementing protein 5	XRCC5_HUMAN	83 kDa	0.0	0.0	0.6	0.0	0.0	0.0	4.0	0.0	6.6	0.461	0.0	0.8	0.0	0.0	1.3	0.879
26S protease regulatory subunit 7	PRS7_BOVIN (+3)	49 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.5	0.0	1.7	0.731	0.0	0.8	0.0	0.8	1.1	0.948
Aspartate aminotransferase, cytoplasmic	AATC_HUMAN (+3)	46 kDa	0.0	0.0	0.6	5.1	0.0	0.0	1.5	0.0	0.3	0.460	0.0	0.0	0.0	0.0	0.0	0.332
Laminin subunit alpha-5	LAMA5_HUMAN	400 kDa	0.0	0.0	0.6	0.0	0.0	1.4	0.4	1.2	5.0	0.179	0.0	1.5	0.0	0.8	3.9	0.334
Protein transport protein Sec24C	SC24C_HUMAN	118 kDa	0.0	0.0	0.6	2.2	0.0	0.0	1.1	2.5	1.3	0.821	0.0	1.5	0.0	1.7	1.1	0.899
Fatty acid-binding protein, epidermal	FABP5_HUMAN	15 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.5	1.2	1.7	0.650	0.0	0.0	0.0	0.8	0.4	0.592
Alpha-2-HS-glycoprotein	FETUA_SHEEP	39 kDa	0.0	0.0	44.8	0.0	64.3	0.0	24.7	0.0	2.0	0.581	80.7	44.0	0.0	0.0	2.8	0.416
E3 ubiquitin/ISG15 ligase TRIM25	TRI25_HUMAN	71 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.1	0.0	0.3	0.541	0.0	0.0	0.0	2.5	0.7	0.800
Serine-threonine kinase receptor-associated protein	STRAP_HUMAN (+2)	38 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.1	0.0	0.7	0.842	0.0	0.0	0.0	0.0	N/A	N/A
Actin-related protein 2/3 complex subunit 4	ARPC4_BOVIN	20 kDa	0.0	0.0	2.4	0.0	0.0	0.0	4.0	0.0	1.6	0.751	0.0	2.3	0.0	0.0	0.9	0.967
Lactoylglutathione lyase	LGUL_HUMAN	21 kDa	0.0	0.0	1.2	0.0	0.0	0.0	3.6	0.0	3.0	0.565	0.0	0.0	0.0	0.0	N/A	N/A
Cell division control protein 42 homolog	CDC42_BOVIN (+2)	21 kDa	1.8	1.1	0.0	0.7	0.0	1.4	1.1	0.0	0.7	0.603	1.4	1.5	1.1	0.0	1.1	0.878
Heterogeneous nuclear ribonucleoprotein H3	HNRH3_HUMAN	37 kDa	0.0	1.1	0.6	1.5	0.0	1.4	1.5	1.2	1.3	0.651	0.0	0.8	1.1	1.7	1.1	0.866
S-phase kinase-associated protein 1	SKP1_BOVIN (+1)	19 kDa	0.0	1.1	0.6	2.2	0.0	0.0	0.4	1.2	0.4	0.333	0.0	0.8	0.0	0.8	0.4	0.316

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
PEST proteolytic signal-containing nuclear protein	PCNP_HUMAN	19 kDa	0.0	0.0	0.6	1.5	0.0	0.0	1.8	1.2	1.5	0.688	0.0	1.5	0.0	1.7	1.5	0.651
Keratin, type II	K2C7_HUMAN	51 kDa	0.0	1.1	0.6	1.5	0.0	0.0	3.6	2.5	1.9	0.501	0.0	0.8	0.0	0.0	0.2	0.163
Glutathione reductase, mitochondrial	GSHR_HUMAN	56 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.5	0.0	1.0	0.993	0.0	0.8	0.0	0.8	1.1	0.948
60S ribosomal protein L36	RL36_HUMAN (+6)	12 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.1	2.5	1.0	0.978	0.0	0.0	0.0	3.3	0.9	0.945
Inorganic pyrophosphatase	IPYR_HUMAN	33 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.5	0.0	1.2	0.924	0.0	0.0	0.0	0.0	N/A	N/A
Thioredoxin domain-containing protein 17	TXD17_HUMAN (+1)	14 kDa	0.0	0.0	1.2	0.0	0.0	0.0	3.3	0.0	2.7	0.588	0.0	0.0	0.0	0.0	N/A	N/A
Programmed cell death 6-interacting protein	PDC6I_HUMAN	96 kDa	0.0	0.0	0.0	4.4	0.0	0.0	2.2	0.0	0.5	0.671	0.0	0.0	0.0	0.8	0.2	0.480
Granulins	GRN_HUMAN	64 kDa	0.0	0.0	0.0	1.5	0.0	1.4	0.4	0.0	1.2	0.875	1.4	1.5	0.0	0.0	2.0	0.548
Hematological and neurological expressed 1 protein	HN1_HUMAN	16 kDa	0.0	1.1	0.6	0.7	0.0	0.0	2.2	0.0	0.9	0.904	0.0	2.3	0.0	0.0	0.9	0.938
NAD(P)H dehydrogenase [quinone] 1	NQO1_HUMAN	31 kDa	0.0	1.1	0.0	2.2	0.0	0.0	1.5	0.0	0.4	0.492	0.0	0.8	0.0	1.7	0.7	0.739
Glutaredoxin-3	GLRX3_HUMAN	37 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.5	1.2	1.8	0.592	0.0	1.5	0.0	0.8	1.6	0.687
Ubiquitin-conjugating enzyme E2 K	UBE2K_BOVIN	22 kDa	0.0	0.0	0.0	2.2	0.0	0.0	2.2	0.0	1.0	0.993	0.0	0.8	0.0	0.8	0.7	0.809
Kinesin-1 heavy chain	KINH_HUMAN	110 kDa	0.0	0.0	0.0	5.1	0.0	0.0	1.1	0.0	0.2	0.492	0.0	0.8	0.0	0.8	0.3	0.542
RuvB-like 1	RUVB1_HUMAN (+1)	50 kDa	0.0	0.0	0.0	0.7	0.0	0.0	2.2	0.0	3.0	0.567	0.0	0.0	0.0	0.0	N/A	N/A
Endoplasmic reticulum resident protein 29	ERP29_HUMAN	29 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	2.3	0.0	0.0	N/A	N/A
Protein arginine N-methyltransferase 1	ANM1_HUMAN (+2)	42 kDa	0.0	0.0	0.0	3.7	0.0	0.0	2.5	0.0	0.7	0.809	0.0	0.0	0.0	0.0	N/A	N/A
Ras-related protein Rab-5C	RAB5C_HUMAN (+1)	23 kDa	0.0	1.1	0.0	0.7	0.0	0.0	1.1	1.2	1.2	0.809	0.0	1.5	1.1	0.0	1.4	0.703
UDP-glucose 6-dehydrogenase	UGDH_HUMAN (+2)	55 kDa	0.0	2.3	0.0	2.9	0.0	1.4	0.7	1.2	0.6	0.611	0.0	0.8	0.0	1.7	0.5	0.457
26S proteasome non-ATPase regulatory subunit 14	PSDE_HUMAN	35 kDa	0.0	0.0	1.2	1.5	0.0	0.0	1.5	0.0	0.5	0.585	0.0	0.8	0.0	0.8	0.6	0.574

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Thymosin beta-10	TYB10_HORSE	5 kDa	0.0	1.1	0.0	0.7	1.1	0.0	0.0	0.0	0.6	0.646	0.0	0.8	4.5	2.5	4.1	0.241
Small nuclear ribonucleoprotein Sm D2	SMD2_BOVIN	14 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.7	0.0	0.3	0.562	0.0	0.8	0.0	1.7	1.1	0.940
Chromobox protein homolog 3	CBX3_HUMAN (+1)	21 kDa	0.0	1.1	0.0	2.2	0.0	0.0	1.1	0.0	0.3	0.391	0.0	0.0	0.0	0.0	0.0	0.212
Actin-1	ACT1_SCHMA	42 kDa	0.0	55.9	53.9	0.0	23.3	0.0	49.7	0.0	0.7	0.660	0.0	67.6	0.0	62.3	1.2	0.845
60S ribosomal protein L3	RL3_HUMAN (+2)	46 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.7	0.0	0.2	0.512	0.0	0.0	0.0	0.8	0.3	0.533
High mobility group protein B1	HMGB1_BOVIN (+4)	25 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.1	0.0	0.4	0.588	0.0	0.0	0.0	2.5	0.8	0.911
C-1-tetrahydrofolate synthase, cytoplasmic	C1TC_HUMAN	102 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.2	0.0	1.5	0.798	0.0	0.0	0.0	0.8	0.6	0.721
Serpin B6	SPB6_HUMAN (+1)	43 kDa	0.0	0.0	0.6	0.0	0.0	0.0	4.4	0.0	7.2	0.454	0.0	0.0	0.0	0.0	N/A	N/A
SH3 domain-binding glutamic acid-rich-like protein 3	SH3L3_BOVIN (+2)	10 kDa	0.0	0.0	0.0	0.0	0.0	0.0	3.3	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Amyloid beta A4 protein	A4_HUMAN (+3)	87 kDa	0.0	0.0	0.0	0.7	0.6	0.0	0.7	2.5	5.1	0.258	0.0	0.0	0.0	1.7	2.3	0.636
Protein-L-isoaspartate(D-aspartate) O-methyltransferase	PIMT_HUMAN	25 kDa	0.0	1.1	0.6	1.5	0.0	0.0	0.7	1.2	0.6	0.502	0.0	1.5	0.0	1.7	1.0	0.987
ELAV-like protein 1	ELAV1_HUMAN (+1)	36 kDa	0.0	0.0	0.6	1.5	0.0	0.0	1.5	1.2	1.3	0.781	0.0	1.5	0.0	1.7	1.5	0.651
Ras-related protein Rab-1B	RAB1B_HUMAN (+3)	22 kDa	0.0	0.0	0.6	0.7	0.0	0.0	1.5	1.2	2.0	0.481	0.0	0.8	0.0	0.8	1.2	0.844
Protein SET	SET_HUMAN (+2)	33 kDa	0.0	0.0	0.0	2.9	0.0	0.0	1.5	1.2	0.9	0.941	0.0	0.0	0.0	2.5	0.8	0.911
40S ribosomal protein S27	RS27_BOVIN	9 kDa	0.0	1.1	0.0	3.7	0.0	0.0	1.5	0.0	0.3	0.421	0.0	0.0	0.0	0.8	0.2	0.337
RuvB-like 2	RUVB2_HUMAN	51 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.5	0.0	2.0	0.680	0.0	0.0	0.0	0.8	1.1	0.935
Reticulocalbin-1	RCN1_HUMAN	39 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	N/A	N/A	0.0	0.8	0.0	0.8	N/A	N/A
Catenin alpha-1	CTNA1_HUMAN	100 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.4	0.0	0.1	0.447	0.0	0.8	0.0	0.8	0.5	0.686

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Vacuolar protein sorting-associated protein 35	VPS35_HUMAN	92 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.5	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
UMP-CMP kinase	KCY_HUMAN (+4)	22 kDa	0.0	0.0	1.2	0.0	0.0	0.0	2.5	0.0	2.1	0.660	0.0	0.0	0.0	0.0	N/A	N/A
Serine/threonine-protein phosphatase 2A catalytic subunit beta isoform	PP2AB_HUMAN (+6)	36 kDa	0.0	0.0	0.6	0.0	0.0	0.0	3.3	0.0	5.4	0.478	0.0	0.0	0.0	0.0	N/A	N/A
Tubulin-folding cofactor B	TBCB_HUMAN	27 kDa	0.0	1.1	0.0	2.2	0.0	0.0	0.7	1.2	0.6	0.594	0.0	0.8	1.1	1.7	1.1	0.939
Cytochrome c	CYC_GORGO (+1)	12 kDa	0.0	0.0	0.0	0.7	0.6	0.0	0.7	0.0	1.7	0.623	0.0	1.5	0.0	0.0	2.1	0.665
Early endosome antigen 1	EEA1_HUMAN	162 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	0.8	0.0	0.8	1.1	0.948
Ras-related protein Rap-1	RAP1_PHYPO	21 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.4	2.5	0.8	0.853	0.0	0.8	0.0	0.8	0.4	0.616
Sorcin	SORCN_HUMAN	22 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.4	1.2	0.5	0.693	0.0	2.3	0.0	0.8	1.1	0.965
Phosphoglucomutase-2	PGM2_HUMAN	68 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	2.5	4.8	0.321	0.0	0.8	0.0	1.7	3.3	0.385
Destrin	DEST_BOVIN (+2)	19 kDa	0.0	0.0	1.2	0.0	0.0	0.0	1.5	0.0	1.2	0.903	0.0	0.8	0.0	0.0	0.6	0.765
Protein disulfide-isomerase A6	PDIA6_HUMAN (+1)	48 kDa	0.0	0.0	0.6	0.0	0.0	0.0	2.5	0.0	4.2	0.507	0.0	1.5	0.0	0.8	3.9	0.334
Coactosin-like protein	COTL1_HUMAN	16 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Keratin, type I cytoskeletal 9	K1C9_HUMAN	62 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.9	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Calcyclin-binding protein	CYBP_HUMAN (+1)	26 kDa	0.0	0.0	0.0	0.7	0.0	0.0	2.5	0.0	3.5	0.537	0.0	0.0	0.0	0.0	0.0	0.391
Twinfilin-2	TWF2_HUMAN	40 kDa	0.0	0.0	0.6	1.5	0.0	0.0	1.1	0.0	0.5	0.597	0.0	0.8	0.0	1.7	1.2	0.876
Astrocytic phosphoprotein PEA-15	PEA15_CRIGR	15 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	1.2	3.2	0.352	0.0	0.8	0.0	0.8	2.2	0.497
PDZ and LIM domain protein 4	PDLI4_HUMAN	35 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.5	1.2	3.6	0.318	0.0	0.0	0.0	0.8	1.1	0.935
Cofilin-2	COF2_BOVIN (+1)	19 kDa	0.0	0.0	4.2	6.6	0.0	0.0	4.4	0.0	0.4	0.445	0.0	3.8	0.0	3.3	0.7	0.650
60S ribosomal protein L21	RL21_HUMAN (+1)	19 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.8	1.2	4.1	0.305	0.0	0.0	0.0	1.7	2.3	0.636

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
UPF0556 protein C19orf10	CS010_HUMAN	19 kDa	0.0	0.0	0.6	0.0	0.6	0.0	1.5	0.0	3.3	0.401	0.0	1.5	0.0	0.0	2.5	0.607
LIM domain and actin-binding protein 1	LIMA1_HUMAN	85 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	1.5	0.0	1.7	2.2	0.497
Actin, cytoplasmic	ACTC_BRABE	42 kDa	0.0	0.0	102.9	0.0	39.4	0.0	94.3	0.0	1.3	0.829	0.0	0.0	0.0	0.0	0.0	0.391
Nascent polypeptide-associated complex subunit alpha, muscle-specific form	NACAM_MOUSE	220 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.7	0.0	0.2	0.485	0.0	0.0	0.0	2.5	0.7	0.800
Hemoglobin subunit beta-C(NA)	HBBN_AMMLE	16 kDa	10.9	0.0	0.0	0.0	0.0	4.3	0.0	0.0	0.4	0.605	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 6	IF6_HUMAN	27 kDa	0.0	0.0	1.2	2.9	0.0	0.0	1.5	0.0	0.3	0.433	0.0	0.0	0.0	0.0	0.0	0.232
Coatomer subunit delta	COPD_HUMAN (+1)	57 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.8	0.0	0.5	0.671	0.0	0.8	0.0	0.0	0.2	0.490
Phenylalanine--tRNA ligase beta subunit	SYFB_PONAB	66 kDa	0.0	0.0	0.0	1.5	0.0	0.0	2.9	0.0	2.0	0.680	0.0	0.0	0.0	0.0	N/A	N/A
Calpain-2 catalytic subunit	CAN2_HUMAN (+1)	80 kDa	0.0	0.0	0.6	0.0	0.0	0.0	3.6	0.0	6.0	0.469	0.0	0.0	0.0	0.0	N/A	N/A
Carbonyl reductase [NADPH] 1	CBR1_HUMAN (+2)	30 kDa	0.0	0.0	0.0	0.0	0.0	0.0	3.3	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Bifunctional glutamate/proline--tRNA ligase	SYEP_HUMAN	171 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.8	0.0	1.7	1.1	0.940
Cystatin-C	CYTC_HUMAN	16 kDa	1.8	0.0	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.182	0.0	0.0	0.0	0.0	0.0	0.182
ADP-ribosylation factor 2	ARF2_BOVIN	21 kDa	0.0	1.1	0.0	2.2	0.0	0.0	1.5	0.0	0.4	0.492	0.0	0.8	0.0	0.0	0.2	0.318
Serine/threonine-protein phosphatase 5	PPP5_HUMAN	57 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.7	0.0	0.3	0.562	0.0	0.8	0.0	0.8	0.7	0.809
26S proteasome non-ATPase regulatory subunit 13	PSD13_HUMAN	43 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.8	0.0	0.8	2.2	0.497
Growth-regulated alpha protein	GROA_HUMAN	11 kDa	0.0	1.1	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.187	0.0	1.5	0.0	0.0	0.6	0.630
Ubiquitin-conjugating enzyme E2 L3	UB2L3_BOVIN (+1)	18 kDa	0.0	0.0	0.6	0.0	0.0	0.0	1.8	0.0	3.0	0.565	0.0	0.0	0.0	0.8	1.4	0.835
PDZ and LIM domain protein 1	PDLI1_HUMAN	36 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.8	0.0	2.5	0.611	0.0	0.0	0.0	0.0	N/A	N/A

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Cystatin-SN	CYTN_HUMAN	16 kDa	0.0	0.0	2.4	1.5	0.0	0.0	0.0	0.0	0.0	0.200	0.0	0.0	0.0	0.0	0.0	0.200
Serine/threonine-protein phosphatase PP1-beta catalytic subunit	PP1B_BOVIN (+1)	37 kDa	0.0	0.0	0.0	0.7	0.0	0.0	2.5	0.0	3.5	0.537	0.0	0.0	0.0	0.8	1.1	0.935
Coatomer subunit alpha	COPA_HUMAN (+1)	138 kDa	0.0	0.0	0.0	3.7	0.0	0.0	1.5	0.0	0.4	0.604	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 3 subunit E-A	EI3EA_XENLA	52 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Cytosol aminopeptidase	AMPL_HUMAN	56 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.9	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
PDZ and LIM domain protein 7	PDLI7_HUMAN	50 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.9	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Lysozyme C	LYSC_HUMAN (+2)	17 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Neutrophil defensin 1	DEF1_HUMAN (+2)	10 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Lysine--tRNA ligase	SYK_HUMAN	68 kDa	0.0	0.0	0.6	0.0	0.0	0.0	1.5	1.2	4.4	0.284	0.0	0.8	0.0	0.8	2.6	0.411
Glutamate dehydrogenase 1, mitochondrial	DHE3_HUMAN (+6)	61 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2	N/A	N/A	0.0	1.5	0.0	0.8	N/A	N/A
Calponin-2	CNN2_MOUSE	33 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.4	0.0	0.2	0.467	0.0	0.0	0.0	0.8	0.4	0.592
Glutamine--fructose-6-phosphate aminotransferase [isomerizing] 1	GFPT1_HUMAN	79 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	1.7	2.3	0.636
Hematological and neurological expressed 1-like protein	HN1L_HUMAN	20 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.5	1.2	N/A	N/A	0.0	0.0	0.0	0.8	N/A	N/A
ATP-binding cassette sub-family E member 1	ABCE1_HUMAN	67 kDa	0.0	0.0	0.0	2.2	0.0	0.0	1.1	1.2	1.1	0.966	0.0	0.0	0.0	0.0	0.0	N/A
Eukaryotic translation initiation factor 4B	IF4B_HUMAN (+1)	69 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.1	0.0	0.7	0.842	0.0	0.0	0.0	0.8	0.6	0.721
Ran-specific GTPase-activating protein	RANG_HUMAN	23 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Septin-2	SEPT2_HUMAN (+2)	41 kDa	0.0	0.0	0.6	0.7	0.0	0.0	0.7	0.0	0.5	0.585	0.0	0.0	0.0	0.0	0.0	0.185

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Interleukin enhancer-binding factor 3	ILF3_HUMAN (+2)	95 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	0.0	0.391	0.0	0.8	0.0	0.0	0.3	0.571
Protein phosphatase 1F	PPM1F_HUMAN	50 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.7	0.0	0.5	0.671	0.0	0.0	0.0	0.0	N/A	N/A
Coatomer subunit gamma-1	COPG1_HUMAN	98 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.7	0.0	0.2	0.512	0.0	0.0	0.0	0.0	N/A	N/A
Complement component C9	CO9_BOVIN	62 kDa	0.0	0.0	0.0	0.0	1.1	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Clusterin	CLUS_BOVIN	51 kDa	0.0	0.0	0.0	0.0	3.9	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Actin-related protein 2/3 complex subunit 3	ARPC3_BOVIN (+1)	21 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.8	0.0	2.5	0.611	0.0	0.0	0.0	0.0	N/A	N/A
Uroporphyrinogen decarboxylase	DCUP_HUMAN	41 kDa	0.0	0.0	0.6	0.0	0.0	0.0	1.1	0.0	1.8	0.715	0.0	0.0	0.0	0.0	N/A	N/A
Keratin, type II cytoskeletal 4	K2C4_HUMAN	57 kDa	0.0	0.0	0.0	0.0	0.0	0.0	4.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Bifunctional purine biosynthesis protein PURH	PUR9_BOVIN	64 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	1.5	0.0	1.7	2.2	0.497
Aminoacyl tRNA synthase complex-interacting multifunctional protein 1	AIMP1_HUMAN	34 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.8	1.1	0.935
Mitogen-activated protein kinase 1	MK01_HUMAN (+2)	41 kDa	0.0	0.0	0.6	0.7	0.0	0.0	1.8	1.2	2.3	0.437	0.0	0.0	0.0	0.0	0.0	0.185
26S proteasome non-ATPase regulatory subunit 1	PSMD1_HUMAN (+2)	106 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.5	0.0	1.0	0.993	0.0	0.0	0.0	0.8	0.6	0.721
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	GBB2_BOVIN	37 kDa	0.0	1.1	0.0	2.9	0.0	0.0	0.0	0.0	0.0	0.238	0.0	0.8	0.0	0.0	0.2	0.322
Histone-binding protein RBBP4	RBBP4_BOVIN (+4)	48 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.8	0.0	0.0	1.0	0.983
Cullin-associated NEDD8-dissociated protein 1	CAND1_BOVIN (+3)	136 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Thioredoxin-like protein 1	TXNL1_HUMAN (+1)	32 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.0	0.0	N/A	N/A	0.0	1.5	0.0	0.0	0.4	0.616

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Nucleosome assembly protein 1-like 1	NP1L1_HUMAN (+2)	45 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Phosphoribosylformylglycinamidine synthase	PUR4_HUMAN	145 kDa	0.0	0.0	0.0	0.0	0.0	0.0	3.3	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Acyl-CoA-binding protein	ACBP_HUMAN	10 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Protein S100-A8	S10A8_HUMAN	11 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Complement C4-A	CO4A_HUMAN (+1)	193 kDa	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Importin-7	IPO7_HUMAN (+1)	120 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.7	1.2	0.9	0.925	0.0	0.0	0.0	0.8	0.4	0.592
Guanine nucleotide-binding protein G(i) subunit alpha-2	GNAI2_HUMAN (+3)	40 kDa	0.0	1.1	0.0	2.2	0.0	0.0	0.0	0.0	0.0	0.212	0.0	2.3	0.0	0.0	0.7	0.743
60S ribosomal protein L23	RL23_AEDAE (+3)	15 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Metalloproteinase inhibitor 1	TIMP1_HUMAN (+2)	23 kDa	0.0	0.0	1.8	0.0	0.6	0.0	1.1	0.0	0.9	0.937	0.0	0.8	0.0	0.0	0.4	0.620
ATP-dependent RNA helicase DDX3X	DDX3X_HUMAN (+1)	73 kDa	0.0	0.0	0.6	0.7	0.0	0.0	1.8	0.0	1.4	0.822	0.0	0.0	0.0	0.0	0.0	0.185
Nuclear autoantigenic sperm protein	NASP_HUMAN	85 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Protein transport protein Sec31A	SC31A_HUMAN (+1)	133 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	0.0	1.5	0.798	0.0	0.0	0.0	0.0	N/A	N/A
Switch-associated protein 70	SWP70_HUMAN	69 kDa	0.0	0.0	0.0	1.5	0.0	0.0	1.8	0.0	1.2	0.888	0.0	0.0	0.0	0.0	N/A	N/A
Rab GDP dissociation inhibitor alpha	GDIA_HUMAN	51 kDa	0.0	0.0	0.0	2.9	0.0	0.0	2.9	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Nicotinamide phosphoribosyltransferase	NAMPT_HUMAN	56 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Cytosolic acyl coenzyme A thioester hydrolase	BACH_HUMAN	42 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Adenosine kinase	ADK_HUMAN	41 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Plasma serine protease inhibitor	IPSP_BOVIN	45 kDa	0.0	0.0	0.0	0.0	2.2	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Aldose reductase	ALDR_HUMAN	36 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.8	0.0	2.5	0.611	0.0	0.8	0.0	0.0	1.0	0.983

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
V-type proton ATPase catalytic subunit A	VATA_HUMAN (+10)	68 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.4	0.0	0.2	0.467	0.0	0.0	0.0	0.0	N/A	N/A
Complement component 1 Q subcomponent-binding protein, mitochondrial	C1QBP_HUMAN	31 kDa	0.0	0.0	0.6	0.0	0.6	0.0	1.1	0.0	2.7	0.431	0.0	0.0	0.0	0.0	N/A	N/A
Interleukin enhancer-binding factor 2	ILF2_HUMAN (+1)	43 kDa	0.0	0.0	0.0	0.0	0.6	0.0	1.5	0.0	N/A	0.239	0.0	0.8	0.0	0.0	N/A	N/A
Leucine-rich repeat flightless-interacting protein 1	LRRF1_HUMAN	89 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	N/A	N/A	0.0	1.5	0.0	0.8	3.2	0.376
Filamin-binding LIM protein 1	FBLI1_HUMAN (+1)	41 kDa	0.0	0.0	0.6	2.2	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	0.0	0.270
N-alpha-acetyltransferase 15, NatA auxiliary subunit	NAA15_HUMAN (+2)	101 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	0.0	0.391	0.0	0.0	0.0	0.0	N/A	N/A
tRNA-splicing ligase RtcB homolog	RTCB_HUMAN (+2)	55 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.7	0.0	0.2	0.512	0.0	0.0	0.0	0.8	0.3	0.533
High mobility group protein B2	HMGB2_BOVIN (+1)	24 kDa	0.0	0.0	0.0	3.7	0.0	0.0	0.4	0.0	0.1	0.435	0.0	0.0	0.0	0.8	0.2	0.500
Sorting nexin-3	SNX3_BOVIN (+1)	19 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.7	0.0	0.5	0.671	0.0	0.0	0.0	0.0	N/A	N/A
Cystatin-B	CYTB_GORGO	11 kDa	0.0	0.0	0.6	0.0	0.0	0.0	1.8	0.0	3.0	0.565	0.0	0.0	0.0	0.0	N/A	N/A
Cathepsin D	CATD_HUMAN	45 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	0.0	1.5	0.798	0.0	0.0	0.0	0.0	N/A	N/A
Heparin cofactor 2	HEP2_MOUSE (+1)	54 kDa	0.0	0.0	0.0	0.0	1.1	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Platelet-activating factor acetylhydrolase IB subunit alpha	LIS1_BOVIN (+5)	47 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.7	0.0	0.3	0.562	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 3 subunit H	EIF3H_HUMAN	40 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.8	0.3	0.533
Adenylate kinase isoenzyme 1	KAD1_HUMAN (+3)	22 kDa	0.0	0.0	0.6	0.0	0.0	0.0	2.5	0.0	4.2	0.507	0.0	0.0	0.0	0.0	N/A	N/A
Ig alpha-1 chain C region	IGHA1_HUMAN (+1)	38 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.9	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
60S ribosomal protein L35	RL35_HUMAN (+7)	15 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Inositol monophosphatase 1	IMPA1_HUMAN (+1)	30 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.8	N/A	N/A
60S ribosomal protein L24	RL24_BOVIN	18 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	0.0	1.5	0.798	0.0	0.0	0.0	0.8	1.1	0.935
Collagen alpha-2(I) chain	CO1A2_BOVIN	129 kDa	0.0	0.0	0.0	0.0	1.1	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Signal recognition particle 9 kDa protein	SRP09_HUMAN (+1)	10 kDa	0.0	0.0	0.6	0.0	0.0	0.0	1.5	0.0	2.4	0.619	0.0	0.8	0.0	0.0	1.3	0.879
Gamma-interferon-inducible protein 16	IF16_HUMAN	88 kDa	0.0	0.0	0.0	2.9	0.0	0.0	0.0	1.2	0.4	0.620	0.0	0.0	0.0	0.0	N/A	N/A
Lumican	LUM_BOVIN	39 kDa	0.0	0.0	0.0	0.0	1.1	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Tight junction protein ZO-2	ZO2_CANFA	132 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Dynactin subunit 1	DCTN1_XENLA	137 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.8	0.4	0.592
Ubiquitin thioesterase OTUB1	OTUB1_HUMAN (+1)	31 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.4	0.0	0.2	0.467	0.0	0.0	0.0	0.0	N/A	N/A
Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase 2	PAPS2_HUMAN	70 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Deoxyuridine 5'-triphosphate nucleotidohydrolase, mitochondrial	DUT_HUMAN	27 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	0.0	1.5	0.798	0.0	0.0	0.0	0.0	N/A	N/A
UTP--glucose-1-phosphate uridylyltransferase	UGPA_HUMAN	57 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.5	0.0	2.0	0.680	0.0	0.0	0.0	0.0	N/A	N/A
Dynactin subunit 2	DCTN2_HUMAN	44 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.7	0.0	0.5	0.671	0.0	0.0	0.0	0.0	N/A	N/A
ATP-dependent RNA helicase DDX1	DDX1_HUMAN (+5)	82 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.4	0.0	0.2	0.467	0.0	0.0	0.0	0.0	N/A	N/A
Niban-like protein 1	NIBL1_HUMAN	84 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Keratin, type II cytoskeletal 5	K2C5_HUMAN	62 kDa	0.0	0.0	0.0	0.0	0.0	0.0	6.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Myeloperoxidase	PERM_HUMAN	84 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Spermidine synthase	SPEE_HUMAN	34 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
ADP-sugar pyrophosphatase	NUDT5_HUMAN (+1)	24 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Deleted in malignant brain tumors 1 protein	DMBT1_HUMAN	261 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Coronin-1B	COR1B_PONAB	54 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Lipocalin-1	LCN1_HUMAN	19 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.2	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
UV excision repair protein RAD23 homolog A	RD23A_HUMAN	40 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Mannose-1-phosphate guanyltransferase beta	GMPPB_HUMAN (+2)	40 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.8	0.4	0.592
Heme-binding protein 2	HEBP2_HUMAN	23 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	0.0	0.0	0.0	N/A	N/A
Actin, clone 302 (Fragment)	ACT3_ARTSX	37 kDa	0.0	0.0	57.5	0.0	17.7	0.0	53.0	0.0	1.2	0.868	0.0	0.0	0.0	0.0	N/A	N/A
DNA replication licensing factor MCM6	MCM6_HUMAN	93 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	0.0	0.0	0.0	N/A	N/A
DNA damage-binding protein 1	DDB1_HUMAN (+7)	127 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 3 subunit I	EIF3I_HUMAN (+2)	37 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.4	0.0	0.2	0.467	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic peptide chain release factor subunit 1	ERF1_BOVIN (+2)	49 kDa	0.0	0.0	0.0	0.7	0.0	0.0	1.1	0.0	1.5	0.798	0.0	0.0	0.0	0.0	N/A	N/A
Alcohol dehydrogenase [NADP(+)]	AK1A1_HUMAN	37 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
CD44 antigen	CD44_HUMAN	82 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
CAD protein	PYR1_HUMAN (+1)	243 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Multifunctional protein ADE2	PUR6_HUMAN (+1)	47 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Calpain-1 catalytic subunit	CAN1_HUMAN	82 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Ig kappa chain C region	IGKC_HUMAN	12 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Adenylosuccinate synthetase isozyme 2	PURA2_HUMAN	50 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Prefoldin subunit 2	PFD2_HUMAN (+1)	17 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform	2AAA_HUMAN (+1)	65 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
N-acetyl-D-glucosamine kinase	NAGK_HUMAN	37 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Nucleophosmin	NPM_HUMAN	33 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	1.7	0.8	0.850
Nucleobindin-1	NUCB1_HUMAN (+2)	54 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Proteasome activator complex subunit 1	PSME1_HUMAN (+2)	29 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Farnesyl pyrophosphate synthase	FPPS_HUMAN	48 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Cytosolic non-specific dipeptidase	CNDP2_HUMAN	53 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.8	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
A-kinase anchor protein 2	AKAP2_HUMAN	95 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Polyadenylate-binding protein 4	PABP4_HUMAN	71 kDa	0.0	0.0	0.0	0.0	0.0	0.0	2.9	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Ran GTPase-activating protein 1	RAGP1_HUMAN	64 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.8	0.6	0.721
EH domain-containing protein 4	EHD4_HUMAN	61 kDa	0.0	0.0	0.0	0.7	0.0	0.0	0.7	0.0	1.0	0.993	0.0	0.0	0.0	0.0	N/A	N/A
Cold shock domain-containing protein E1	CSDE1_HUMAN	89 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.4	0.0	0.2	0.512	0.0	0.0	0.0	0.0	N/A	N/A
KH domain-containing, RNA-binding, signal transduction-associated protein 1	KHDR1_HUMAN (+2)	48 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	1.5	0.0	0.0	N/A	N/A
26S proteasome non-ATPase regulatory subunit 6	PSMD6_HUMAN	46 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.7	0.0	0.5	0.671	0.0	0.0	0.0	0.0	N/A	N/A
Spleen trypsin inhibitor I	BPT2_BOVIN	11 kDa	0.0	0.0	0.6	0.0	1.7	0.0	0.0	0.0	2.7	0.584	0.0	0.0	0.0	0.0	N/A	N/A
Ribosome-binding protein 1	RRBP1_HUMAN	152 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

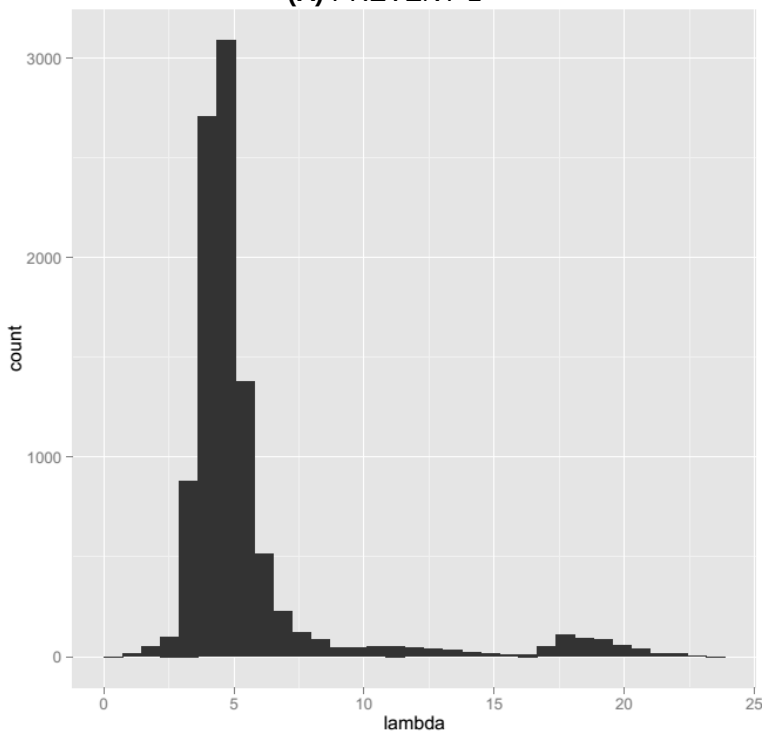
Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Small nuclear ribonucleoprotein Sm D3	SMD3_HUMAN	14 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
S-methyl-5'-thioadenosine phosphorylase	MTAP_HUMAN	31 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Ribosome maturation protein SBDS	SBDS_HUMAN	29 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Polypyrimidine tract-binding protein 1	PTBP1_HUMAN (+4)	57 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Cytoplasmic dynein 1 light intermediate chain 1	DC1L1_HUMAN	57 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Cysteine--tRNA ligase, cytoplasmic	SYCC_HUMAN	85 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
ATP-dependent DNA helicase Q1	RECQ1_HUMAN (+1)	73 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 1b	EIF1B_HUMAN (+2)	13 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Prolactin-inducible protein	PIP_HUMAN	17 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Azurocidin	CAP7_HUMAN	27 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Sorting nexin-6	SNX6_HUMAN (+2)	47 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Alcohol dehydrogenase class-3	ADHX_HUMAN	40 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
HLA class I histocompatibility antigen, B-73 alpha chain	1B73_HUMAN (+4)	40 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Vasodilator-stimulated phosphoprotein	VASP_HUMAN	40 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
cAMP-regulated phosphoprotein 19	ARP19_HUMAN (+3)	12 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Periostin	POSTN_HUMAN	93 kDa	0.0	0.0	0.0	0.0	1.7	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Transcription elongation factor B polypeptide 2	ELOB_HUMAN (+1)	13 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

Identified Proteins (668)	Accession Number	Molecular Weight	1	2	3	4	1	2	3	4	Fold	P-value	1	2	3	4	Fold	P-value
Serum deprivation-response protein	SDPR_HUMAN	47 kDa	0.0	0.0	0.0	2.2	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Antileukoproteinase	SLPI_HUMAN	14 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Peroxiredoxin-5, mitochondrial	PRDX5_HUMAN (+4)	22 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Keratin, type I cytoskeletal 14	K1C14_HUMAN	52 kDa	0.0	0.0	0.0	0.0	0.0	0.0	6.2	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Acidic mammalian chitinase	CHIA_BOVIN	52 kDa	0.0	0.0	0.0	0.0	1.1	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Actin-related protein 2/3 complex subunit 5-like protein	ARP5L_HUMAN (+3)	17 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Glucosamine-6-phosphate isomerase 1	GNPI1_HUMAN (+1)	33 kDa	0.0	0.0	0.0	0.0	0.0	0.0	1.1	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Eukaryotic translation initiation factor 4 gamma 1	IF4G1_HUMAN (+1)	175 kDa	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Prefoldin subunit 5	PFD5_HUMAN	17 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Adapter molecule crk	CRK_HUMAN (+2)	34 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A
Major vault protein	MVP_HUMAN (+3)	99 kDa	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.0	N/A	N/A	0.0	0.0	0.0	0.0	N/A	N/A

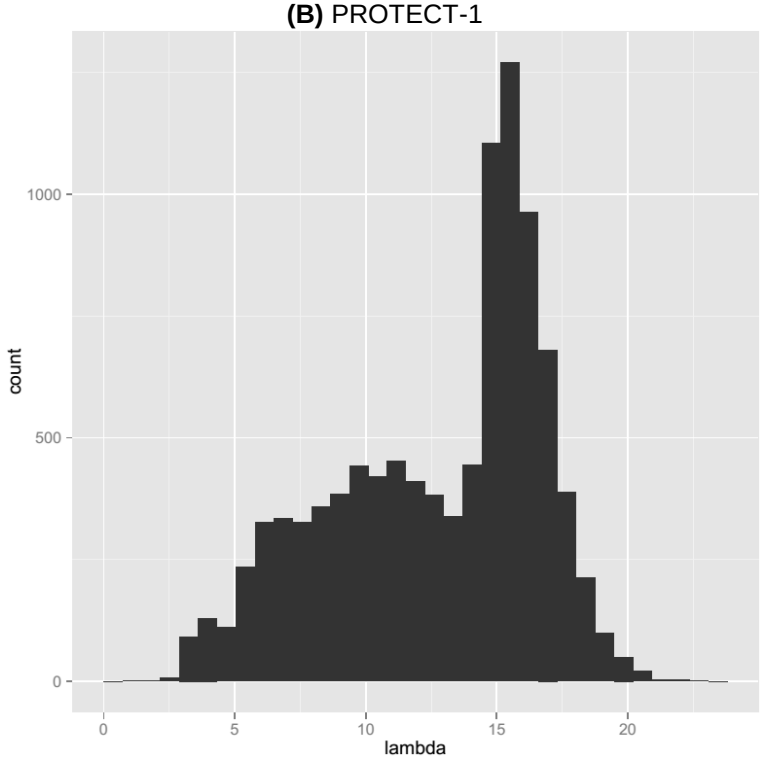
P values were derived from unpaired Student t tests with unequal variance.
"NA" denotes "not applicable"
(note that every time protein expression in the majority of samples from 1 of the 2 groups compared was undetectable, the t test was not performed)

Supplementary Figure 1. Distribution of tuning parameters λ1 from ten thousand 5-fold likelihood cross-validations of penalized logistic regression of associations of serum miRNA concentrations with incidence and progression of diabetic retinopathy.

(A) PREVENT-1

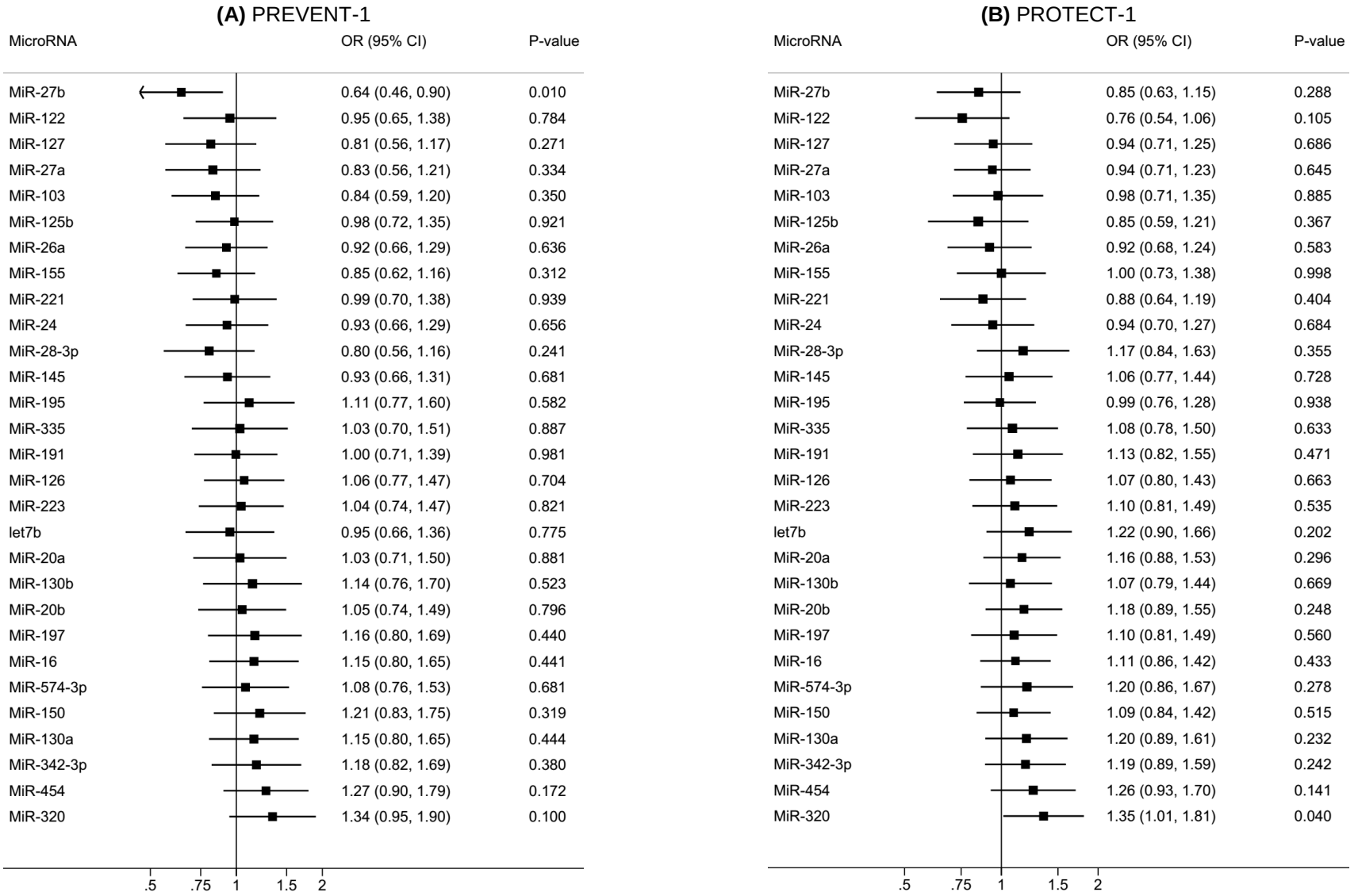


(B) PROTECT-1



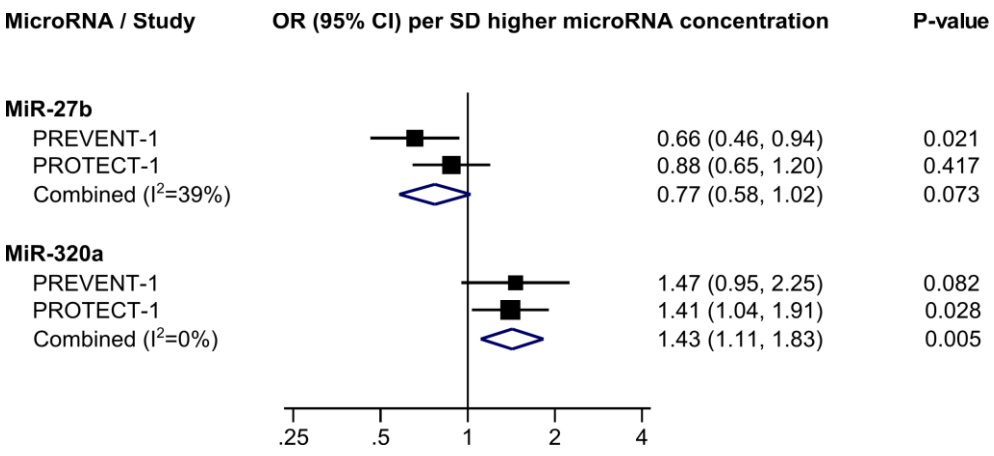
The median lambda value was 4.60 in PREVENT-1 and 14.21 in PROTECT-1.

Supplementary Figure 2. Association of miRNAs with diabetic retinopathy, adjusted for age, sex and diastolic blood pressure.

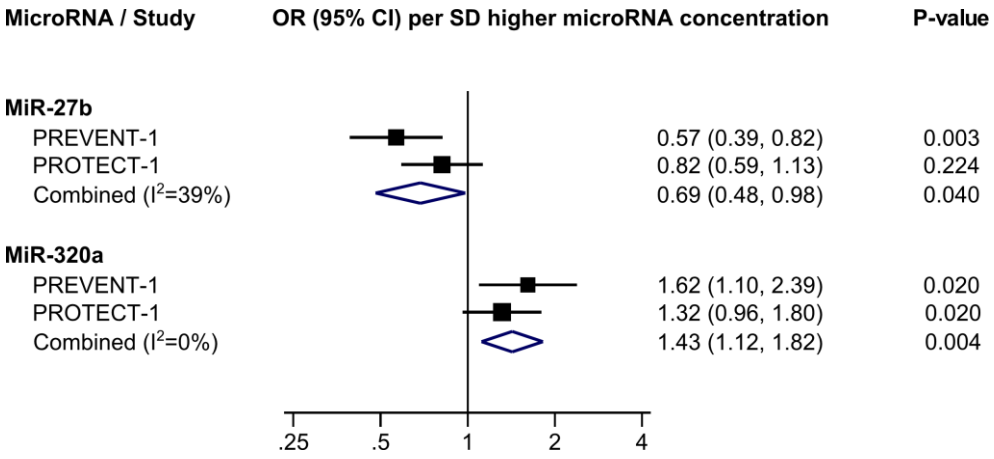


Supplementary Figure 3. Sensitivity analysis of the penalized logistic regression analysis of the association of serum miRNA concentrations with diabetic retinopathy.

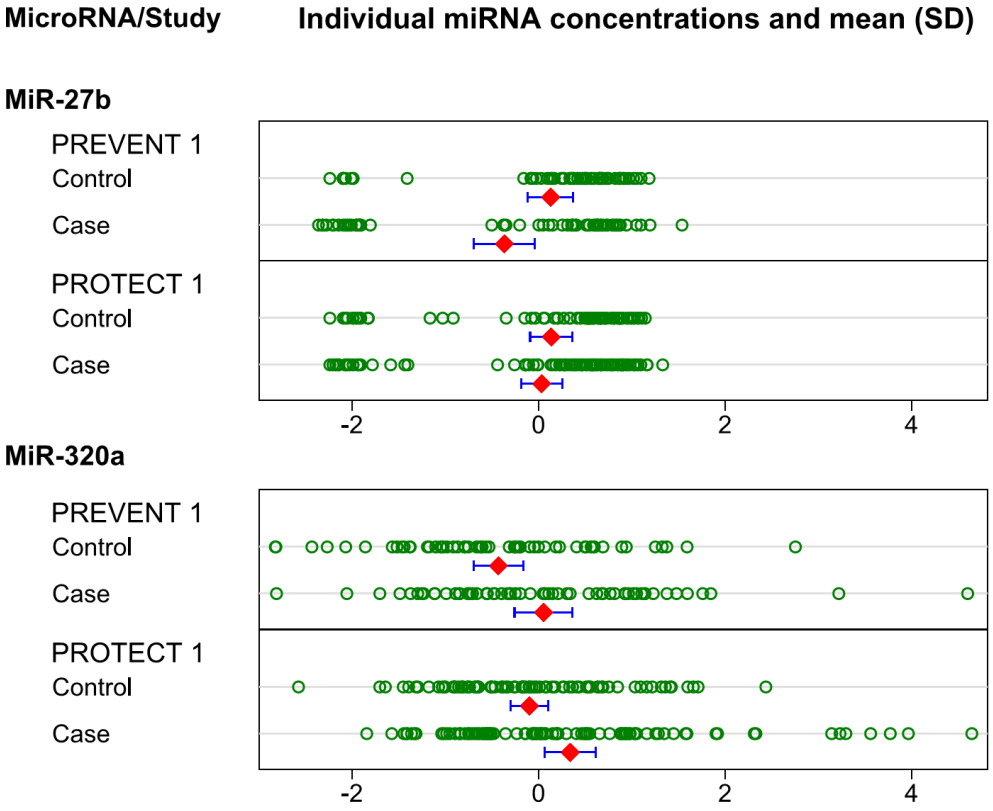
(A) Standardizing C_t values to the global C_t average (instead to cel-miR-39)



(B) Excluding cases with microalbuminuria

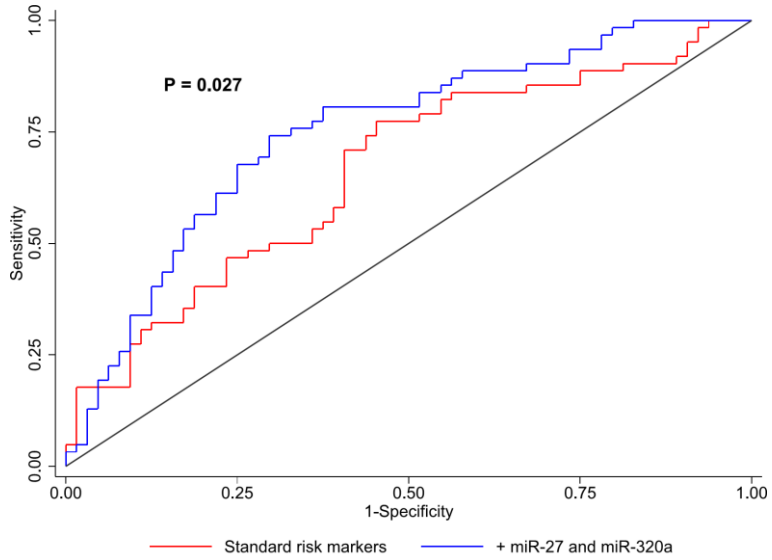


Supplementary Figure 4. Comparison of normalised serum concentrations of miR-27b and miR-320a. The plot depicts concentrations for individual participants (in green), plus a summary estimate with mean (in red) and 95% confidence interval (in blue).

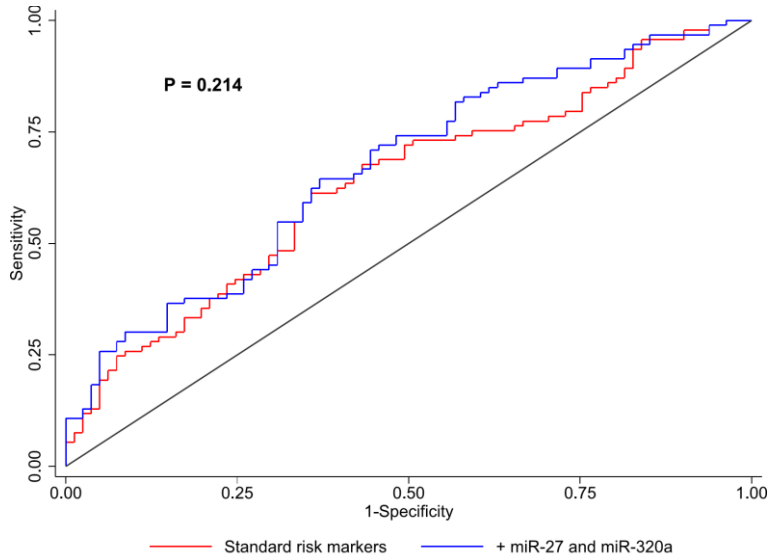


Supplementary Figure 5. Added predictive value of miR-27b and miR-320a for diabetic retinopathy as an adjunct to standard risk markers.

(A) PREVENT-1



(B) PROTECT-1



Standard risk markers subsume age, sex, duration of diabetes, diastolic blood pressure, and level of HbA_{1c}. The areas under the curve for standard risk markers and standard risk markers plus miR-27b and miR320a were 0.662 (95% CI: 0.566, 0.757) and 0.749 (0.663, 0.835) for PREVENT-1 (Δ 0.087, P=0.027), and 0.634 (95% CI: 0.551, 0.712) and 0.668 (0.558, 0.748) for PREVENT-1 (Δ 0.034, P=0.214).